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THE RENAL LESION IN BRIGHT'S DISEASE

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THE RENAL LESION
IN
BRIGHT'S DISEASE

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THOMAS ADDIS
Professor of Medicine, Stanford University

JEAN OLIVER
Professor of Pathology, Long Island College of Medicine;
Formerly Professor of Pathology, Stanford University

WITH 170 FULL PAGE PLATES, 2 IN COLOR
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TO
WILLIAM OPHÜLS

CONTENTS

PAGE
LIST OF PLATES ix

LIST OF TEXT ILLUSTRATIONS xi

CHAPTER
I. INTRODUCTION 1

II. CLINICAL METHODS 7
THE PURPOSE OF THE CLINICAL METHODS—Nature of the Renal Lesion—Extent of the Renal Lesion—TECHNIC OF THE CLINICAL METHODS.

III. CLINICAL DEFINITIONS 39
URINE VOLUME—Urine Volume after Abstention from Fluids—Urine Volumes after Water Drinking—Volume Quotient—SPECIFIC GRAVITY OF THE URINE—High Specific Gravities—BLOOD UREA CONCENTRATION—Relation between the Blood Urea Concentration and the Amount of Functioning Renal Tissue—BLOOD PRESSURE

THE RATIO: $\dfrac{\text{RATE OF UREA EXCRETION IN ONE HOUR}}{\text{BLOOD UREA CONCENTRATION}}$

URINARY SEDIMENT.

IV. A CLINICAL CLASSIFICATION OF BRIGHT'S DISEASE IN ACCORDANCE WITH THE NATURE OF THE RENAL LESION 69
HEMORRHAGIC BRIGHT'S DISEASE—Initial Stage—Latent Stage—Active Stage—Terminal Stage—DEGENERATIVE BRIGHT'S DISEASE—ARTERIOSCLEROTIC BRIGHT'S DISEASE.

V. THE PATHOLOGICAL METHODS 101
PURPOSE OF THE PATHOLOGICAL METHODS—TECHNIC OF THE PATHOLOGICAL METHODS.

VI. PATHOLOGICAL DEFINITIONS 113
CLOUDY SWELLING—FATTY DEGENERATION—NECROSIS—ATROPHY OF THE EPITHELIUM—HYPERTROPHY OF THE EPITHELIUM—REGENERATION OF TUBULAR EPITHELIUM—TUBULAR CASTS—AMYLOID DEGENERATION—TUBULAR OBLITERATION AND ITS RESULTS—INFLAMMATORY PROCESSES—GLOMERULITIS—ARTERIOSCLEROSIS AND ENDARTERITIS—SCLEROSIS OF GLOMERULI—CONGESTION OF THE KIDNEY—METALLAXIS.

VII. THE CLINICAL AND PATHOLOGICAL OBSERVATIONS 171
HEMORRHAGIC BRIGHT'S DISEASE—Active Stage—Latent Stage—Terminal Stage—DEGENERATIVE BRIGHT'S DISEASE—Cryptic Form—Pyogenic Form—Bacterial Form—Non-bacterial Form—ARTERIOSCLEROTIC BRIGHT'S DISEASE.

CHAPTER PAGE
VIII. Clinical Summary and Comparison of Clinical and Pathological Data . 531
IX. A Correlation of the Clinical and Pathological Observations. . . . 543
Hemorrhagic Bright's Disease—Initial Stage—Active Stage—Latent Stage—Terminal Stage—Degenerative Bright's Disease—Cryptic Form—Pyogenic Form—Non-bacterial Form—Arteriosclerotic Bright's Disease.

X. A Theoretical Description of the Course and Sequence of the Pathological Processes in Bright's Disease 557

XI. A Classification and Theory of Bright's Disease. 581

References. 598

LIST OF PLATES

PLATES PAGES
I A–XV B. Low and high power photomicrographs of the active stage of hemorrhagic Bright's disease 176–243
XVI A–XX B. Low and high power photomicrographs of the latent stage of hemorrhagic Bright's disease 248–267
XXI A–XLV B. Low and high power photomicrographs of the terminal stage of hemorrhagic Bright's disease 274–393
XLVII A–LI B. Low and high power photomicrographs of degenerative Bright's disease, cryptic form 398–421
LII A–LVI B. Low and high power photomicrographs of degenerative Bright's disease, pyogenic form 426–447
LVII A & B. Low and high power photomicrographs of degenerative Bright's disease, bacterial form 452, 453
LVIII A–LIX B. Low and high power photomicrographs of degenerative Bright's disease, non-bacterial form 460–467
LX A–LXXII B. Low and high power photomicrographs of arteriosclerotic Bright's disease 472–527
LXXIII. Degenerative Bright's disease, early stage of pyogenic form . . . 603
LXXIV. Degenerative Bright's disease, non-bacterial form 604
LXXV. Degenerative Bright's disease, early cryptic form 605
LXXVI. Degenerative Bright's disease, cryptic form with necrosis of epithelium 606
LXXVII. Degenerative Bright's disease, late cryptic form, with regeneration of epithelium 607
LXXVIII. Degenerative Bright's disease, non-bacterial form 608
LXXIX. Degenerative Bright's disease, late stage of pyogenic form . . . 609
LXXX. Arteriosclerotic Bright's disease, general view 610
LXXXI. Arteriosclerotic Bright's disease, early glomerular fibrosis . . . 611
LXXXII. Arteriosclerotic Bright's disease with afferent arteriole 612
LXXXIII. Arteriosclerotic Bright's disease, fibrosis of tuft 613
LXXXIV. Arteriosclerotic Bright's disease with inflammatory lesion . . . 614

LIST OF PLATES

PLATES		PAGES
LXXXV.	Arteriosclerotic Bright's disease with degenerative lesions of epithelium	615
LXXXVI.	Arteriosclerotic Bright's disease, cysts in cortex	616
LXXXVII.	Arteriosclerotic Bright's disease, renal failure casts	617
LXXXVIII.	Hemorrhagic Bright's disease, active stage with hemorrhage. (*Color*)	618
LXXXIX.	Hemorrhagic Bright's disease, active stage, intracapillary form	619
XC.	Hemorrhagic Bright's disease, active stage, crescent formation	620
XCI.	Hemorrhagic Bright's disease, active stage, necrosis of tufts	621
XCII.	Hemorrhagic Bright's disease, active stage, late extracapillary form	622
XCIII.	Hemorrhagic Bright's disease, latent stage	623
XCIV.	Hemorrhagic Bright's disease, terminal stage with involvement of afferent and efferent vessels	624
XCV.	Hemorrhagic Bright's disease, terminal stage with glomerular adhesions	625
XCVI.	Hemorrhagic Bright's disease, terminal stage with fibrosis of glomeruli	626
XCVII.	Hemorrhagic Bright's disease, terminal stage with congestion of vessels. (*Color*)	627
XCVIII.	Hemorrhagic Bright's disease, terminal stage with renal failure casts	628

LIST OF TEXT ILLUSTRATIONS

FIGURE PAGE
1. Decrease in variability of ratio with increase in blood urea concentration 26
2. Relation between ratio and weight of kidneys in animals. 29
3. Constancy of ratio at varying levels of blood urea concentration. 30
4. Relation between volume quotient and amount of secreting tissue in kidney . . . 47
5. Specific gravity of varying concentrations of urea, sodium chloride and sodium acid phosphate. 50
6. Percentage frequency distribution of specific gravity of night urine in normal individuals after restriction of fluids. 51
7. Distribution of 278 blood urea concentration observations 54
8. Relation between the blood urea concentration and the amount of functioning renal tissue. 56
9. Provisional separation of ratios obtained in adults into those which can be regarded as within limits of normal variation, those beyond these limits and those which cannot be described as either normal or abnormal. 62
10. Course of development of hemorrhagic Bright's disease 74
11. Renal failure casts and hyaline and fatty casts of ordinary breadth 84
12. Extent of lesion in Arteriosclerotic Bright's disease. 97
13. Cloudy swelling with granules of both the small and large "droplet" form in adjacent tubules 116
14. Mitochondria of original and regenerated epithelium 127
15. Urea content of original and regenerated epithelium. 130
16. Formation of a blood cast 136
17. Renal failure casts in situ 139
18. Focal embolic lesion from a case of bacterial endocarditis 155
19. Amount of renal tissue in Case VI, hemorrhagic Bright's disease, active stage. . 202
20. Changes in amount of functioning renal tissue in Case XV, hemorrhagic Bright's disease, active stage. 240
21. Changes in amount of functioning renal tissue in Case XXXVII, hemorrhagic Bright's disease, terminal stage 349

CHAPTER I

INTRODUCTION

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THE RENAL LESION IN BRIGHT'S DISEASE

CHAPTER I

INTRODUCTION*

At the meeting of the Association of American Physicians in 1929, Dr. Henry Christian said: "As clinicians I think we should recognize that we may be unable during life to predict accurately whether the pathologist is going to find more or less nephrosis or less or more nephritis; in other words, we are still in the same predicament in which we have always been, unable to use a pathological classification of nephritis that can be applied easily and accurately in the clinic."[1] In these words he summarizes the attitude of a generation of investigators. It is, for instance, identical in spirit with the conclusion reached by Schlayer in 1923[2] when he says after a lifetime experience of experimental and clinical work:

> "Der eine Fundamentalsatz nach dieser Richtung lautet: die Nierenfunktion an sich ist in ihrer Veränderung unabhängig von der anatomischen Art der Erkrankung: . . . Die zweite Erfahrung nach dieser Richtung sagt: Es besteht keine feste Beziehung zwischen diffuser Erkrankung und Funktionsänderung . . . Nach der dritten Erfahrungstatsache endlich können sich anatomisch ganz gleichartige Schädigungen unter ganz verschiedener Funktionsweise demonstrieren: . . . Wird doch unser praktisches Handeln vielfach viel mehr von der richtigen Erkennung des Funktionszustandes der Niere als von der Erkennung der Art der anatomischen Erkrankung, welche diesem zugrundeliegt, beeinflust."

These men are leaders of clinical investigation in Bright's disease who, all their lives, have sought with care for some measure of correlation between clinical and anatomical facts. From them the recognition of a wide discrepancy has a significance much deeper than the comparatively light-hearted and sometimes cynical acquiescence of the pathologist who has his own independent field of labor. It has all the weight of a confession of frustration exacted by hard and inescapable facts and, as such, it deserves a very special respect and consideration.

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* T. A.

This present situation cannot, of course, be summed up as one of any complete failure. It is not at all that during the past thirty years of clinical work no fuller insight has been gained, but rather that medicine has been following a path which leads away from morphology. Many clinical investigators are still inclined to regard the divergence of medicine and structural pathology as a deliverance from an unnecessary incubus. They eagerly use the recently developed clinical procedures for the determination of various substances in the blood or urine as a means towards the elucidation of the action of the kidney in disease and hope that an understanding of the "pathological physiology" of the kidney will suffice as a foundation for diagnosis and treatment. Their attitude is summed up in the often-repeated remark: "It is more important to know what the kidney does than to know what it looks like." Their practice has led to the elaboration of clinical tests of what is called the "function" of the kidney, but the results of these tests are regarded as an end in themselves; functional abnormality is not expected to tally with any corresponding structural defect. Their unspoken thought seems to be that after all it is unreasonable to expect a somewhat old-fashioned morphology to keep pace with the advances promised by these new fine tools of medicine. But it is already almost sure that their clinical tests have no more lasting value than the quite provisional physiological hypotheses on which they are based and that their hopes were from the first unwarranted because our conceptions as to the physiology of the kidney are quite naturally as childish and incomplete as is our knowledge of its structure.

The return of medicine from "function" to the straight and narrow road of morphology was initiated in 1914 by the publication of Volhard and Fahr's book "Die Brightschenierenkrankheit." They again subjected clinical prediction to the test of correspondence with objectively ascertained structural fact, as Bright and Bartels had done before them, and again there came to workers in this department of medicine a sense that there was sure ground beneath their feet, and that progress was possible and measurable however hard the way might be. That, as a matter of fact, the progress made has not been so striking as to command universal acknowledgement is sufficiently shown by our opening quotations; yet we believe it has been a true progress, one which need never be retraced. But apart altogether from differences of opinion as to what has been actually accomplished, Volhard and Fahr again set before clinicians Bright's ideal of an explanation of disease "by a reference to morbid anatomy,"* a service to the time in which they wrote that can scarcely be overvalued.

The purpose of this monograph is identical with the purpose of Volhard and Fahr's book.[3] It is a comparison of clinical and pathological facts made with the intention of determining the degree of correlation between them. But the field which it covers is not nearly so broad because we have excluded all direct consideration of extrarenal facts. We are dealing, then, not with Bright's disease but only with the *renal lesion* in Bright's disease. The reason for this restriction is that the clinical "facts" which have been collected are the results of methods designed for the determination of the nature and extent of the renal lesion. These results are in terms which permit of a direct comparison with the morphological facts. They are quantitative numerical results which can be compared with the structural renal changes which also, in theory at least, are reducible to number. Extrarenal lesions have been noted, but the attempted correlation between the clinical and the pathological facts has been confined to the kidney. Further, many facts of purely clinical observation not strictly relevant to the discussion have been excluded. This could the more safely be done since, with only one or two exceptions, all the patients were directly under the care of the clinical author, all the histories were taken by him, and all the physical examinations were made by him. In addition, all the counts of casts and cells were made by the clinical author and the measurements of the amount of functioning renal tissue were carried out in the laboratory under his immediate supervision. The entirely individual nature of the work has of course greatly limited its scope, and lack of time has sometimes made the observations incomplete, but in compensation such facts as were ascertained may have something of the unity to be expected of work done by one individual with one end in view.

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* The subtitle of Bright's "Medical Cases," published in 1827, is, "illustrating the symptoms and cure of diseases *by a reference to morbid anatomy*."

In order to make the clinical and pathological comparison representative of a general experience all the patients whose kidneys were obtained have been included no matter how slight and incomplete the clinical observations might sometimes be. The collection has been made over a period of ten years, and includes patients from a time when the methods for the determination of the nature of the renal lesion were only in course of development. Even so the number of cases is not large. Permission for postmortem examination is obtained only with difficulty in this locality and many of the patients whose progress had been followed to the end most completely and for the longest time are excluded from this review because we were not allowed to study their kidneys after death.

CHAPTER II

CLINICAL METHODS

CHAPTER II

CLINICAL METHODS*

THE PURPOSE OF THE CLINICAL METHODS

Any clinical study of Bright's disease leads always to an accumulation of facts, all interesting in themselves, but for the most part disconnected and inexplicable. The pursuit has always had, of course, that interest which is derived from the observation of the fate and fortune of individual human beings living under the curse of an obscure malady, but to the more abstract and generalized view it is a deeply discouraging subject for reflection. One cannot with any reasonable hope commence again the mere accumulation of observations. That has been done so often during the past century by masters of observation. One may of course accept the facts and reclassify and rearrange them in the hope that some workable hypothesis may emerge from the confusion. There are more facts to fit together than before, or at least we are able to define them more exactly. For a hundred years it has been known that in certain cases of the disease there is sometimes a lipemia, and at the end an accumulation of urea in the blood, but we can now determine the urea and fat content in milligrams per 100 c.c. We have a multitude of clinical tests which, when the disease is already far advanced, tell us that the rate of excretion of various substances is decreased. We can measure easily and quite exactly the level of systolic and diastolic pressure, and have greatly increased our knowledge of the mechanics of the circulation. But with all this new exactitude it cannot be said that there has come much new light. The old problems of the relationship between the renal, vascular, nervous, and general tissue changes still remain. There is no general agreement in regard to classification, no certain knowledge as to etiology and no foundation for prognosis. The more one sees of the disease the more difficult and involved does it appear, for in every patient is comprised a tangle of problems which seem only loosely related. The only reasonable conclusion is that this is going to be a long and difficult matter, and that there is apparently little to be gained by speculation in regard to the total complexity.

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*T. A.

It seems more hopeful to focus attention on one aspect or another of the disease and for the time being to neglect the others. If this is to be done there can be little doubt as to which side of the matter should be first attacked. For, historically, the whole problem came first into being with Bright's recognition that bilateral non-suppurative renal lesions were constantly associated with proteinuria and rightly or wrongly the lesion in the kidney has since then come to be regarded as central. But of really decisive importance is the fact that among all the perplexities of this disease it is the renal lesion which gives promise of being least impervious to clinical investigation. The kidney is the only organ of the body whose secretion may be readily obtained, and it seems reasonable to suppose that structural changes in the kidney may be paralleled by corresponding anatomical alternations in the urine. For the time being, therefore, we arbitrarily abstract from Bright's disease all but the renal lesion, and we do so because we are thus freed from the questions which by their number and impenetrability paralyze endeavor. We are left with a single concrete problem, the problem of determining the relation between observed changes in the urine during life and the structural abnormalities found in the kidney after death, exactly the problem set before us by Richard Bright.

But though the question is old the methods used for its solution must be new, new at least in the sense that they should be more specifically fitted to the purpose of the investigation. If that is the case they can well afford to be useless and inappropriate for more general clinical purposes. Now, in general, the question under discussion belongs to morphology. We are attempting to predict morphological changes in the kidney, and so the clinical methods must also be of a morphological nature and the results must be expressed in strictly morphological terms.

The general problem involves two distinct but related questions in morphology. In the case of any renal lesion we desire to know first its *nature* and second its *extent*. What sort of a lesion and how much of a lesion are both morphological questions but the methods required for their solutions are very different.

1. Nature of the Renal Lesion. Bright separated the group of diseases associated with his name from all others by finding that the urine contained a heat coagulable protein. It was the work of his immediate successors further to refine this separation, and it was by a microscopical examination of the urinary sediment that this was done. An additional criterion for the diagnosis of Bright's disease was established. Not proteinuria alone but proteinuria and cast formation was required. With these signs the nature of the renal lesion in Bright's disease is already broadly defined. It is that sort of a lesion in which protein from the blood plasma passes through the kidney into the urine and it is also that sort of a lesion which damages but does not at once altogether disintegrate the architecture of the kidney. Casts, being moulds of the interior of the tubules, demonstrate the maintenance of at least the essential elements of the form and function of the renal elements within which they have their origin. They are not formed when the lesion is of the nature of a suppurative process or partakes of the nature of a new growth, for such lesions destroy the renal tissue and obliterate all its individual characteristics. But in Bright's disease the lesion is of such a nature that it can become a part of the life of the kidney, entering into all the intricacies of its structural and functional reactions.

But clinical medicine has not yet found the means whereby the nature of the renal lesion can be defined much more precisely than by such general statements. There is no accepted method by which it can be directly studied. The inferences drawn are based not on observations on the urine but on general experience and on facts which do not relate directly to the kidney. Such inferences are surest when they rest on a knowledge of the etiology of the lesion. Thus if it is known that the patient has attempted suicide by taking corrosive sublimate the nature of the renal lesion is known from general experimental and pathological experience, or if the patient develops hematuria, hypertension and edema during convalescence from tonsillitis, general clinical experience affords some basis for prediction. But it will be noted that these predictions rest on general grounds, not on specific measurements made on the kidneys of the particular individual patient. And when, as in a great number of cases, there is no observation or history in regard to etiology, either no conception of the nature of the renal lesion is formed at all, or it is a shrewd guess derived subconsciously from a synthesis of many phenomena, none of them bearing any constant relation to the nature of the renal lesion, but in their sum total pointing with some degree of probability towards the truth. In other realms of medicine this ancient and unteachable wisdom will always be required, but here it will not need to be invoked if direct and quite objective methods can be devised. Indeed, in this small matter clinical intuition is particularly powerless, so that even masters of the art are frequently misled. They are misled because of the great variability of the manifestations of Bright's disease in the different tissues and organs of the body so that it is seldom safe to deduce the state of the kidney from observations on the vascular, hemopoietic or nervous systems, or wise to form a judgment as to the predominant renal lesion even from the sum of all that by means of present clinical methods is seen, felt, or surmised. But, principally, they are misled because for many years they themselves have ceased to study the urine which comes from the diseased kidneys of their patients. They deal only with symbols transmitted to them by hurried and machine-like technicians, although within that urine which they never see is contained all the direct evidence as to the nature of the renal lesion.

For it is an error to suppose that an inflammatory renal lesion, for instance, is necessarily associated with hypertension. Every clinician knows that during long stages in the development of glomerular nephritis hypertension may be absent, and has known instances in which from start to finish it has not shown itself. Even where, as in the retina, it is possible to observe the progression of disease in the arteries and arterioles, it is especially those who have had experience who are most sure that apparently identical lesions are to be seen both in glomerular nephritis and in renal arteriosclerosis. It is not true that it is only in the end stages of glomerular nephritis that a severe secondary anemia is apt to appear. The same phenomenon is observed along with the entirely different degenerative renal lesion associated with amyloid disease. A soft pitting edema associated with a reduction in the protein concentration of the plasma is characteristic of the degenerative renal lesion which now is usually called nephrosis, but it is much more often seen during a certain stage in the progression of glomerular nephritis, and this is also true of the inversion of the relative proportions of albumin and globulin in the plasma, of the cholesterinemia, and of the lipuria.

And finally it is no longer necessary to show that no great insight into the nature of the renal lesion is to be gained from any test of renal function or from a combination of any number of these tests. Thirty years ago that was still a hope but the truth of the words of Schlayer which we have quoted have within that period received abundant illustration. All these signs and symptoms, and very many others, may, it is true, be taken as indicating in a general way the probable nature of the renal lesion. For a tendency exists towards the association of certain symptom groups with certain renal lesions, but since it is only an average statistical relationship one may be led far astray in individual cases. And it must be so because these signs and symptoms are not linked to the renal lesion in any causal sense. It is as though they on the one side and the renal lesion on the other were separate and independent results of a more deeply lying complex of conditions. Furthermore it would appear as though this hypothetical complex was no fixed and rigid system but must contain variable factors. It is only so that we can account for the frequent lack of correspondence in renal as opposed to extrarenal effects. For from within the experience of any clinician who has been seriously interested in Bright's disease for any considerable length of time it would be possible to abstract a series of cases which would form a nearly continuous series passing from those in which only evidences of a renal lesion were found, through all degrees of mixture of renal and extrarenal effects and ending in those in whom a renal lesion as such could hardly be said to exist.

It is at least universally admitted that renal and extrarenal symptoms vary greatly in relative intensity and even their occasional almost complete dissociation is conceded. To suppose that they are associated but independent results of a more deeply lying web of causative factors is only to adopt the simpler hypothesis. For if we say that the renal lesion is the basic factor and that all extrarenal effects such as hypertension, arteriosclerosis and edema are the results of the renal lesion, we find ourselves in that welter of subsidiary hypotheses and assumptions which comprise such a large proportion of the literature of Bright's disease. It is safer to conceive as causal only those associations which are invariable. When we find much protein and many casts in the urine we invariably find a renal lesion and, conversely, when renal lesions of a certain type are demonstrated at post-mortem examination an adequate first-hand examination of the urine during life has always revealed casts and protein in the urine. Such symptoms may therefore be regarded as belonging to the series which we call renal symptoms. Are there any others which we can clearly follow as further elements in the series: renal lesion → proteinuria and cast formation? Perhaps, but not as yet quite clearly, nor with any certainty that such further consequences lie quite solely within the renal series. But in some cases we may think of it as continued. If the loss of protein from the body is very great, the protein in the plasma may be decreased and the osmotic pressure of the plasma reduced. We can understand then how the flow of fluid from the tissue spaces into the capillaries might be retarded and we can regard the particular type of edema which occurs under such circumstances as belonging to the extended series: renal lesion → proteinuria → reduction in plasma protein → lowered osmotic pressure of plasma → edema. So also we look on anemia as a necessary result of any large hemorrhage but are we so sure of the mechanism of the anemias associated with long-continued relatively slight losses of blood from the body? It is true that they often disappear when the bleeding is stopped, but nevertheless the pathogensis may be complex and include a defect in blood formation as one of the necessary factors. So here also clinical experience does not give us any warrant to conclude that loss of protein from the body is always or even often the sole cause of this special type of edema.

If we survey the entire array of all examples of Bright's disease, that is to say of all types of renal lesion which are of such a nature as to lead to proteinuria and cast formation, the rarity of any consequences other than those seen in the urine becomes apparent. We must of course remember that the idea of Bright's disease which we derive from postmortem examination experience is highly distorted and that even the conception formed from clinical experience in hospital wards is quite inadequate. Only a very small proportion of all people with Bright's disease ever lie on a postmortem table or even in a hospital bed. Probably even now the majority of all instances of Bright's disease remain unknown and unsuspected. It is only through the recent and still increasing prevalence of the custom of examining the urine of apparently normal individuals that we are beginning to appreciate the wide prevalence of the disease and the great variety of its forms and to understand how relatively infrequent is that type of lesion which is irreversible and progressive or which carries with it any apparent consequence for the life of the individual. But however much one may be impressed with the silence of the great majority of renal lesions it remains true that there are some which in the end destroy so large a proportion of the renal tissue that uremia supervenes. Apart from the urine then there are two possible consequences: In the vast majority healing with or without defect, in the few death from renal failure. Clinicians cannot afford to wait for either of these consequences.

In order to learn directly about the nature of the renal lesion we must therefore neglect all that is clinically interesting because of its complexity, we must turn aside from all problems which are of immediate importance for the welfare of the patient. We are left alone with the urine. If any enlightenment is possible it is only from the urine that it can come. And so the problem is stripped of hope and interest. Why should there be any hope when a study which began a century ago has borne so little fruit and has at last fallen into such disrepute that it is no longer thought worthy of the personal attention of the physician? Are not the writings of the authorities in this field full of warnings as to the fallacies of conclusions based on observations of the urinary sediment? Why should there be any interest when we are debarred from the use of all the new and beautiful applications of the methods of physics and of chemistry? For these also are taken away. A renal lesion is only a structural deviation from the normal architecture of the kidney. So it is entirely a question of anatomy. The methods used in this investigation must be derived from the old technic of cellular pathology, and if any answer to the question is obtained it will be expressed in strictly anatomical terms.

It seems reasonable to suppose that there should be a relation between the nature of the lesion in the kidney and the morphology of the urinary sediment. This was the original hope of the early investigators but their work ceased when their hypothesis failed to receive any confirmation. It was found that the urinary sediment was much more variable than any renal lesion could well be thought of being. Even in the same patient examined at different periods during the same day it could be seen that casts would be present in one specimen of urine and absent in the next. Hypotheses as to temporary retention followed by the elimination of "showers of casts" were advanced but, whatever the explanation, it was plain that no reliance could be placed on such a bizarre symptom. Again, it was frequently, in fact usually observed that the patients who had the most severe renal lesions were the very ones in whose urine no casts could be found, so that there almost seemed to be an inverse relation between the severity of the lesion and the abnormality of the sediment. All such facts, met at the very outset of any work on urinary sediments, were decisive in discouraging any further investigation along these lines.

Nevertheless this curiously irregular behavior of casts seemed to be a phenomenon quite worthy of study for its own sake. It was not long before it was observed that the specimens of urine in which casts were absent were always of low specific gravity, and it was then found that casts could be made to disappear from the urine of any patient who drank enough water to produce a low specific gravity urine. When casts were centrifuged off from urine and after washing in salt solution suspended in solutions of varying sodium chloride concentration, one type of cast, the hyaline variety, disappeared when the concentration fell below a certain critical point. But this point varied with the hydrogen ion concentration of the solution, so that it required a higher and higher concentration of salt to keep the hyaline casts from dissolving the more alkaline the solution became. It was clear then that there was a simple physical explanation for the irregularity of appearance of hyaline casts, the type of cast which almost always far outnumbers all others. But the epithelial, granular and waxy casts do not dissolve and their disappearance during the course of a diuresis must have a different explanation. The simplest, of course, is that when there is a relatively rapid flow of urine down the tubules the conditions are unfavorable for the agglutination of cellular material to form casts. We have, then, clear evidence of a difference in the physical properties of casts. The hyaline casts (and under this catagory are included all casts whose matrix is of hyaline material, no matter what cellular, fatty or granular matter may happen to have been included during their formation) have the properties of a protein compound of chondroitin-sulphuric acid. The cellular type of cast on the other hand, and this includes epithelial casts and their granular and waxy derivatives, has the properties which are common to cell-masses and on this account may be found in urine whose salt concentration and hydrogen ion concentration are so low as to lead to the solution of the hyaline variety.

The significance of these facts in connection with the relation between the morphology of the kidney and of the urine is at once apparent. We know now why no constant relation was to be found between the renal lesion and cast formation. It is for the same reason that no constancy can be observed in another evidence of a pathological process in the kidney, in the rate of red blood cell excretion in the urine. The commonly used "fragility" test for red blood cells which shows that they disappear in certain dilutions of sodium chloride is enough to suggest that in certain dilutions of urine they might also vanish. The reasonable hypothesis of a constant relation between the nature of the renal lesion and the morphology of the urine had been rejected because the conditions under which the urinary examinations had been made were frequently of such a nature as to destroy the very evidences on which the comparison was to be based. There was no need then to be inhibited by the failures of the past. All that was needed for an adequate testing of the hypothesis was to find the conditions favorable for cast formation and for the production of a urine in which all the structures derived from the kidney might be preserved.

The salt concentration of urine can be varied at will by variation in water intake. In order to produce a concentrated urine it is sufficient to abstain from water and urine secreted during sleep is almost always acid. The necessary conditions were therefore met by abstention from fluids during the day and by the collection of night urine. There is one clinical state, however, in which the urine remains dilute even when fluids are not taken. When the blood urea concentration has risen to high levels no hyaline casts can be found, only the epithelial varieties remain and they have a breadth which indicates that they have been formed in the wide lower reaches of the collecting tubule system. In all other states, however, the conditions can be complied with and it is found that the discouraging variability in the urinary sediment is no longer to be found.

But more than this is necessary. It was found that merely qualitative observations of the urinary sediment were only now and then decisive. There are indeed certain individual structures to be found in urine which have an unequivocal significance. Blood casts (not only the blood casts of the textbooks but also the yellow or orange casts full of granules or agglutinated masses in which no traces of the original structure of the red blood cell remain) show that there has been bleeding in the kidney and into the tubules. What we at first called "oval fat bodies" but which we now know are greatly swollen and degenerated tubule cells, indicate the presence of a degenerative process within the kidney. A sediment in which most of the casts are broad casts of the epithelial variety is a sure indication of true uremia.[4] But in most cases nothing so decisive is discovered, the differences are quantitative, not qualitative, and then it is only through quantitative differentiation that the meaning of the facts can be determined.

Now it happens that quantitative methods can easily be applied to the urine which yield results whose certainty and significance transcend those which can ordinarily be obtained in other body fluids. It is within the memory of this generation with what fresh interest and clarity the study of the blood and cerebrospinal fluid was pursued when methods for the enumeration of their cellular units and for the determination of their chemical constituents were introduced into medicine. But such methods can yield only ambiguous results, for they determine only concentrations and the concentration of any cell or substance may vary on account of changes in the total volume of the blood or cerebrospinal fluid as well by virtue of a change in the total number of the cells or the total amount of the dissolved substance. The effort spent on the development of methods for the measurement of the total blood and plasma volume shows that this defect is clearly recognized. But when we work with urine we are delivered from all this uncertainty. It would be palpably absurd and meaningless to deal with concentrations in a fluid whose volume is so variable. Here it is easy to determine rates of excretion per unit of time and thus to deal with quantities which are perfectly clear and unambiguous.

After the very simple technic described in a later section had been developed it was applied to the study of the urine of normal individuals. Quite unexpected results were obtained. It has been generally supposed that casts and red blood cells are present in the urine only when the kidney is involved in some quite definitely pathological process. But in the urine of apparently healthy students we found protein and casts and red blood cells. This transforms the diagnosis of Bright's disease. It can no longer rest on a qualitative basis for there is no qualitative difference between the urine of patients and the urine of normal individuals. It becomes a quantitative diagnosis. Those individuals have Bright's disease who have more protein and a greater number of casts than are to be found in the urine during health.

The determinations were made on 74 medical students. The average rate of cast excretion was 1040 per twelve hours with a range of from 0 to 4270. These were hyaline casts with very rare epithelial casts. The rate of red blood excretion averaged 65,750 per twelve hours and varied from 0 to 425,000. The white blood cells and epithelial cells had an average of 322,550 per twelve hours and ranged from 32,400 to about 1,000,000. Protein was present in amounts which probably varied between 10 and 30 mg. per twelve hours.[5]

These quantities may be used for a clinical definition of Bright's disease in terms which, though arbitrary, have a measurable statistical significance. We have taken values which lie outside the range of normal variation, a rate of protein excretion of more than 30 mg. per twelve hours and a rate of cast excretion in excess of 5000 casts per twelve hours. Any value which such a definition may possess exists of course solely for the clinician and only for the reason that it rests on readily ascertainable objective clinical measurements which are directly related to an essential lesion in Bright's disease.

2. Extent of the Renal Lesion. The term "extent" denotes the amount of renal tissue which has been rendered functionless by the disease process. It is not intended to designate the degree to which the lesion is localized or diffused throughout the kidney. For instance, the extent of the lesion would be the same whether the inactivity were due to a local atrophy of certain areas in the kidney or were the result of a diffuse lesion which diminished the total capacity of all the renal elements to an equal

degree. Nor has the word any meaning in connection with the intensity or quiescence of the lesion or with its reversibility or irreversibility. It is intended simply to indicate the amount of renal tissue which in any way whatsoever has ceased to work. It is a morphological measurement attained indirectly through a measurement of function. The clinical problem as to how this is to be accomplished is a particular instance of the more general question of the relation between the function and structure of the kidney.

There is an obvious distinction between structure and function. But a preoccupation with either one or the other is apt to make us forget that in the living body form and function are inseparately related since both are aspects of the one life process. Those who have been long engaged in puzzling over the inconsistencies of renal function come to feel, by contrast, that the structure of the kidney must be something steady, lasting and solid. But it is not really so. There is no fixed amount of renal tissue in any organism. There is, it is true, a statistically determinable relation between the mass of the kidney and the mass of the body. But let the food be altered so that more protein is consumed and it will be found that the kidney has increased in size, just as it will be found to be smaller if the food consists mainly of carbohydrate and fat. The structure of the kidney is not, as is the structure of some part of a machine, relatively fixed and unalterable. It is a living part of a living organism and waxes and wanes in accordance with the needs of the organism as a whole.

During the past few years the investigations of A. N. Richards and his collaborators[6] have revealed an interesting analogy between the kidney and the heart. There is a slow systole and diastole of the glomeruli. The total function however is continuous, for the kidney is a multiple organ and while one group of renal elements is resting another is active. If the quantity of material brought to the kidney for excretion increases, the number of actively functioning renal elements is increased and the total mass of active renal tissue is thus augmented. But this seems to be only a temporary device to meet temporary emergencies. For if the need for increased work continues there is an increase in the size of the cells, particularly of the cells of proximal convoluted tubules, as if there were a regulation local to the kidney which maintained an optimum relation between the rest and the activity of its elements through an increase or decrease in the total mass of renal substance.

These general considerations have an immediate clinical interest and importance but at present clinicians no longer hope that their clinical tests can determine such a gross matter as the total amount of functioning renal tissue. Their hope is fixed on function divorced from structure, on a function which has been dissected into many partial functions, each with its appropriate test, in the expectation that through their combination a complete picture of the mode of action of the kidney may emerge. But function alone is an unsatisfying abstraction and our disregard of structure is really the result of a despair of the possibility of being able to determine structure through function. There seems to be good reason for despair. Thus when one kidney is excised, that is to say half of the total kidney tissue removed, there is no appreciable change in the rate of excretion of the various urinary constituents, the composition of the blood is undisturbed, and if such tests of function as the phenolsulphonephthalein test are used no inkling of the loss is given. If half the renal tissue of the body can be removed without altering the total function how can we ever hope to predict the amount of renal tissue from our functional tests? This lack of correspondence between structure and function is of course only an appearance. The doubling of the work of the remaining kidney has increased the number of its actively functioning renal units and the total amount of active tissue is as great after the operation as before. But this is a hidden internal adaption which escapes our measurements.

However the mere discussion of these difficulties is sufficient to suggest the way by which they may be circumvented. No engineer would measure the horsepower of an engine which was idling, so why should we be content with measures of function which fluctuate below their full values in accordance with the sub-maximal and ever changing requirements of ordinary life? As in the matter of the determination of the nature of the renal lesion, so here in regard to the question of its extent, the difficulties resolve themselves into a search for the appropriate conditions under which to carry out the measurements. One of these is already obvious. We must waken the kidney to its full activity so that as far as possible all the renal elements may be working and all the glomeruli may be flushed with blood. And there is another still more important requirement. Neither the function nor the structure of the kidney can be separated from its environment. Neither has any separate existence in itself. Both are the product of the environment and both are continually altering in adjustment with it. And so we can learn nothing sure about the kidney unless we know this environment. The blood is the immediate environment of the kidney and all effective means for the measurement of function must start with a determination of the condition of the blood and evaluate the performance of the kidney in relation to this measure.

These are the general conditions. The rest is a matter of convenience and can be worked out in detail in different ways. We chose urea as a test substance, because it can be determined with accuracy in the blood and urine. When any specific substance such as urea is selected it is a simple matter to measure the volume of blood which has been freed of the substance by the kidney per unit of time. All that is necessary is a measurement of the rate of urea excretion over a convenient length of time, say one hour, and a determination of the concentration of urea in the blood during that hour. Suppose that we find that each 100 c.c. of blood contains 50 mg. of urea and that during one hour 2500 mg. of urea are excreted. That means that 5000 c.c. of blood have been freed from urea, for each 100 c.c. of blood only contains 50 mg. and in order to get 2500 mg. into the urine $^{2500}/_{50}$ or 50 times 100 c.c. of blood must have been used. This measure is free of dependence on any theory as to the manner in which urea is excreted. If there is no reabsorption of urea then the volume of glomerular urine would also be 5000 c.c. per hour, but the volume of blood freed from urea per hour would still be 5000 c.c. even though the tubules subtracted urea from the glomerular fluid or added to it by urea secretion. It is an objective measure of the work done by the kidney in relation to an actual measurement of the specific environment by which it is determined.

The last statement requires some elucidation. The urea concentration of the blood is no doubt a particularly important part of the environment with respect to urea excretion but it has not been shown that it is the only governing factor. In fact we have direct evidence that under ordinary conditions it is by no means the only factor, for even in the same individual the rate of urea excretion may vary between wide limits even though the blood urea concentration remains constant.[7] We can produce variations in the rate of urea excretion independent of blood urea concentration by food and drink and exercise[8] and we have experimental evidence that the rate may be under a twofold hormonal control, since it may be increased by minute quantities of adrenalin, decreased by very small amounts of pituitrin and left unaffected by the injection of a mixture of adrenalin and pituitrin.[9] It is only true in a general statistical sense that the rate is controlled by the blood urea concentration. In actual experience the rate is constantly fluctuating above or below the average value for any given blood concentration in obedience to a multitude of known and unknown factors in the environment.[10] We had then to seek for those special conditions under which the urea concentration of the blood becomes the all-important factor. These were gradually defined mainly by trial and error. For instance after a considerable number of determinations of the ratio between the hourly rate of urea excretion and the blood urea concentration had been determined at varying levels of blood urea concentration it was found that the variability of the ratio diminished as the blood urea concentration increased. (Fig. 1.)

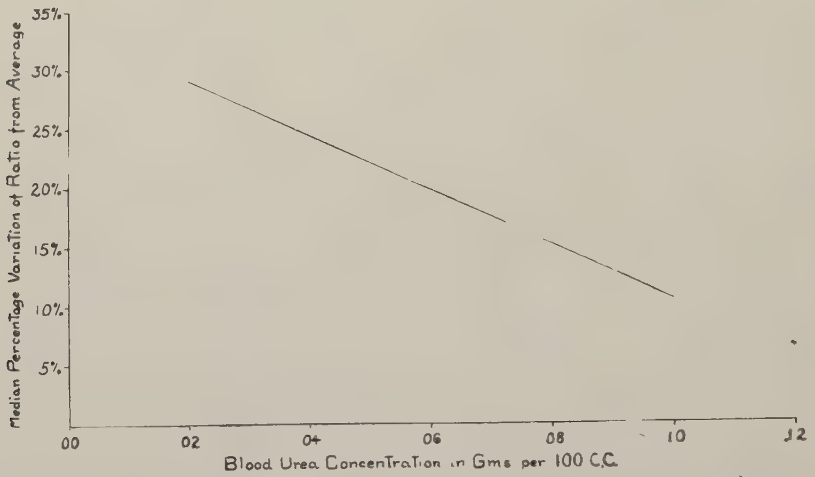

FIG. 1. Decrease in variability of ratio with increase in blood urea concentration.

Urea is a non-toxic substance and enough can be taken to so increase the blood urea concentration that the relative importance of all other factors is markedly diminished. But it was found that the constancy we desired became more and more marked as the time after the administration of the urea lengthened. For the first hour and a half the blood urea concentration is rising and at this period and for some time afterwards the ratio values are considerably more variable than if the observations are carried out at a later period when the blood urea concentration, if other conditions are constant, is slowly falling along a curve which approximates a straight line[11] (Table 1).

TABLE I

EFFECT ON THE RATIO: $\frac{\text{RATE OF UREA EXCRETION}}{\text{BLOOD UREA CONCENTRATION}}$ OF THE TIME ELAPSING BETWEEN THE ORAL ADMINISTRATION OF UREA AND THE MEASUREMENT OF THE RATIO

Time from administration of urea to mid-point of period of urine collection, minutes	Number of observations	Ratio: $\frac{\text{rate of excretion}}{\text{blood concentration}}$	Rate of excretion: mg. urea per hour	Blood concentration: mg. urea per 100 c.c.
15	14	37.5	1834	50
45	14	56.1	4120	74
75	14	48.5	3950	82
105	14	47.1	3662	79
135	14	46.2	3451	76

The conditions which we finally adopted as the best involved the taking of urea dissolved in 1000 c.c. of water at 6 A.M. (20–30 gm. if the blood urea concentration was within normal limits, proportionately less if it was above normal). No food was taken and every hour up to and including 11 A.M. 500 c.c. of water were drunk. Three separate ratio determinations were made between 9 A.M. and 12 noon, and averaged. These conditions comprised then the production of a very marked activity of the kidney through the administration of large quantities of urea and water, the accentuation of the importance of the blood urea concentration as the controlling factor in the determination of the urea excreting work of the kidney by the increase in blood urea concentration, and finally a uniformity in the general conditions and an absence of all such accessory factors as are involved in the consumption of food.

The degree of correspondence between this functional method and the amount of renal tissue was tested in several different ways. The method was here at a disadvantage for it was necessary to use rabbits, not human beings, and we have never succeeded in attaining anything approaching the constancy of the ratio in individual human beings. It seems likely that a real constancy in the environment of the kidney is inconsistent with the forcible administration of urea and water by stomach tube, and the repeated catheterizations and bleedings which cannot be avoided in animals. The first test was made in 1916 and was really one of the observations through which the necessary conditions of the method were defined.[12] The ratio between the rate of urea excretion and the blood urea concentration was determined in rabbits before and after ligation of one ureter, and it was found that a depression of the ratio value after the operation was found only when urea was given. The second test was carried out in 1917 and was an attempt to determine the value of the method for the determination of the extent of a renal lesion. Lesions of a varying degree of severity were produced in rabbits by uranium and the clinical and pathological conclusions in regard to the severity of the lesion were compared.[13] The clinical results of course could be ranged in order of magnitude, but in the anatomical observations it was only possible to separate the kidneys into three classes, those with slight, those with moderate and those with severe lesions. In 24 comparisons the functional and anatomical classifications independently carried out agreed in 22 and this was the only functional method by which a close correspondence was attained. At a later date the method of unilateral nephrectomy was again resorted to and was combined with a careful measurement of the hypertrophic compensatory structural changes. After an interval of time had elapsed following the operation the prediction derived from the ratio measurements indicated that the remaining kidney had 79 per cent of the original renal tissue while the anatomical measurements showed that it possessed 82 per cent of the original value.[14]

The most direct test was carried out in 1923.[11] Measurements of the urea ratio were made on rabbits varying in size from the smallest to the largest we could obtain. They were then killed and the kidneys weighed. The ratio values are shown plotted against the kidney weights in Figure 2.

The results, though, as might be expected, not very consistent, are in consonance with the idea that there is a straight line relation between the magnitude of the ratio and the weight of the kidneys. Finally, the reliability of the method was measured in man.[15] If the conception that there is a constant relation between this measure of function and the amount of functioning tissue is correct, then in the same individual living under constant conditions and possessing therefore approximately the same quantity of kidney tissue from day to day, the value of the ratio: rate of urea excretion ÷ blood urea concentration, observed under the required conditions ought also to be approximately constant. The results shown in Figure 3 were measured in the same individual under the standard conditions except that the quantity of urea administered was varied.

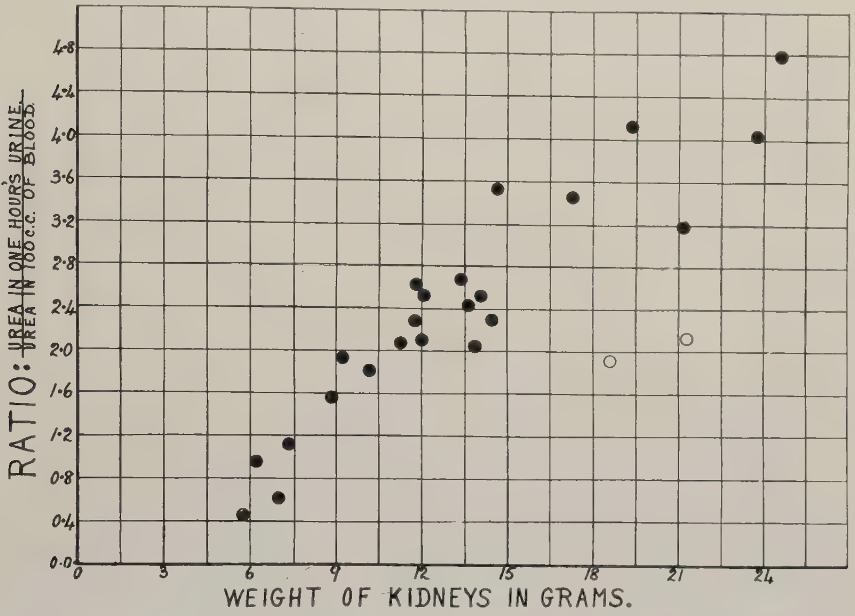

FIG. 2. Solid dots indicate relation between ratio and weight of kidneys in animals whose renal tissue was normal or almost normal. Circles show relationship in rabbits 24 and 25, whose renal secreting tissue had been in part destroyed by spontaneous nephritis.

The results indicate that under these special conditions the rate of urea excretion varies nearly exactly as the blood urea concentration; in other words the measured factor in the environment of the kidney is the controlling and all-important factor. The resulting approximate constancy of the ratio measurements is in conformity with the structural constancy which may be assumed to have existed in this individual during the period over which the measurements were made. A somewhat better agreement was observed in another individual when the blood urea concentration was kept at about the same levels as in the work with patients.[16]

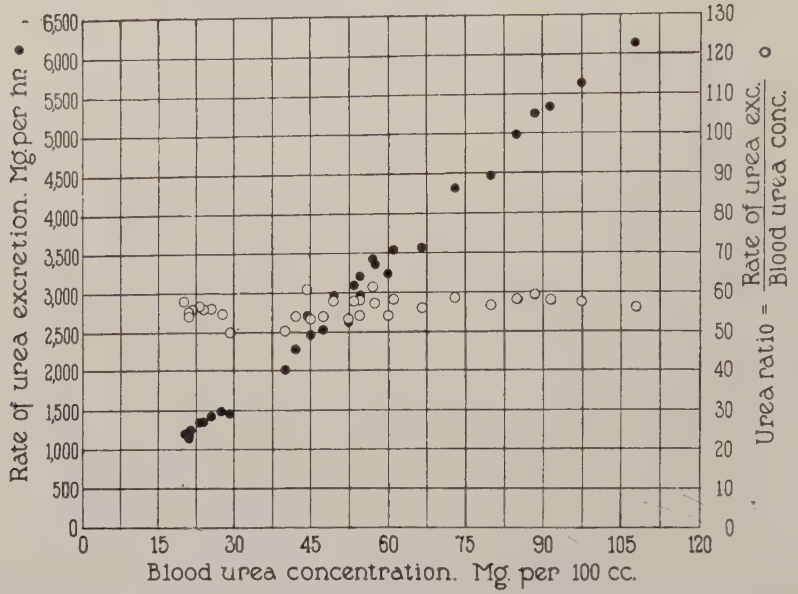

FIG. 3. Constancy of ratio in same individual at varying levels of blood urea concentration. Dots indicate rates of urea excretion, circles ratio values.

There never was of course any doubt that the total function of the kidney might be used as a measure of the total mass of its secreting elements. But there was doubt as to whether it would be possible at once to develop a method in which the correlation between function and structure would be sufficiently close to be of practical value in clinical investigation. However, at least this measure of success has been attained. During the course of Bright's disease we can follow all the major changes in the extent of the renal lesion. This is of particular value in those patients in whom the lesion has not rendered more than half the renal tissue functionless. In such cases the usual clinical functional methods leave us entirely in the dark as to the direction in which the lesion is progressing. But with this method we can plot the whole history of the increase or the decrease in the extent of the lesion from its inception to its termination.

Technic of the Clinical Methods

The primary purpose was a comparison of certain quantitative clinical measurements with the extent and nature of the renal lesion but it was essential that these should be related to the qualitative clinical facts elicited by the usual methods of examination. A good deal of time was therefore spent in recording the patient's history and in describing the evolution of the symptoms. Particular pains was taken in trying to reconstruct the conditions which had preceded the onset of the disease in those patients in whom the time of onset was known. In the histories given here only the facts which can reasonably be regarded as relevant to our present purpose have been set down.

The usual physical examination was then made. In certain cases where there was uncertainty as to the size of the heart and aorta members of the *x*-ray laboratory gave us a 2 meter chest plate, and an attempt was sometimes made to outline the shadow of the kidneys, or to study the condition of the walls of the large arteries. In some patients also in whom ophthalmoscopic examination of the retinal arteries left room for doubt, an expert opinion was given by members of the eye clinic. Very occasionally the basal metabolism was measured or some other special method was used outside the laboratory. But all the patients with the exception of terminal cases were seen in the laboratory, and it was there that the history and all the other clinical data were obtained.

After the history and physical examination the patient was given a wide-necked rubber-stoppered bottle containing a trace of formaldehyde with written instructions as to the method of urine collection. Up to within the last few years the time of collection was set from 6 P.M. to 6 A.M., but since then the patient has been told to write down on the label on the bottle the time at which urine is voided before going to bed, and again to write down the time at which the urine is collected directly into the bottle when he rises from bed next morning. If a few minutes are spent in making this clear to the patient we have good reason to know that quite accurately timed collections will be obtained. The patient is also given detailed instructions not to take fluids of any sort from after breakfast until the collection is completed next morning.

In those cases in which a measurement of the amount of functioning renal tissue was made the patient took urea (in quantity sufficient to raise the blood urea concentration to above 60 mg. per 100 c.c.) in about 1000 c.c. of water at 6 A.M. No breakfast was given. At 7 A.M. and 8 A.M., after voiding urine he drank 500 c.c. of water. The urine voided at about 9 A.M., 10 A.M., 11 A.M., and 12 noon was collected in the laboratory and exactly timed. Blood was obtained at the mid-point between each urine collection. After each voiding of urine 500 c.c. of water were drunk. The three ratios between rate of urea excretion and blood urea concentration were averaged. The result is the number of 100 c.c. quantities of blood freed from urea in one hour.

In 163 ratio determinations carried out on 31 normal individuals, none of whom deviated far from the usual height and weight of adults, the average value was 50.4 or 5040 c.c. of blood freed from urea in one hour. The coefficient of variability for the group was 13 per cent but in individuals the variability was as low as 4 per cent.

In individuals living under approximately constant conditions the weight of the kidneys tends to vary as the body size, and we knew from experience that when there was a notable difference in body size the volume of blood freed from urea was always greater in the larger individual, so that there was reason to suppose that a correction for body size would reduce the variability. At the time however we were not certain which measure of body size was most closely related to kidney size. Later, we discovered that the kidney weight varied more closely with the body surface than with the body weight or body length, and we then corrected the ratio values observed in patients in accordance with their body surface. In our group of normals whose average body surface was 1.82 sq.m. the 5040 c.c. per hour becomes 2770 c.c. per hour per square meter. The value obtained in the patient is given as a percentage of this average normal value.

The method has obvious clinical limitations. In most patients with edema it is impossible even by these means to evoke a pronounced diuresis, and in patients with failing hearts or with very high levels of diastolic pressure it should not be used at all. It has its sure place in the study of those most numerous ambulatory patients who still retain more than one-third of the usual amount of renal tissue. In these cases the ordinary "renal function tests" give negative or uncertain results, and it is in them that a true picture of the progression of the lesion can be obtained by a repetition of the test from time to time. But in the last stages when the amount of effective renal tissue becomes less than one-third of normal it is unnecessary to subject patients to this test for, as has been shown by E. M. MacKay and L. L. MacKay[17] the degree of increase in blood urea concentration comes to be a fair measure of the decrease in kidney size.

While these measurements are being made the concentrated night urine is thoroughly mixed by repeated inversion of the rubber-stoppered bottle and a 10 c.c. sample is transferred to a special graduated tube, and centrifugalized for five minutes at 1800 revolutions per minute. The supernat~~e~~nt a urine is decanted and pipetted down to a known volume which varies with the amount of sediment as judged by direct observation. The casts and cells are thoroughly mixed in this remaining fluid by means of a capillary pipette and drops are transferred to a hemocytometer. The casts are counted under the low power microscope in several unit volumes of 0.0009 c.c., the number depending on the concentration. The cells are counted in unit volumes of 0.0001 c.c. with a ⅙ eyepiece and no. 10 objective. The calculation is very simple if a slide rule is used. The rates of cast, red blood cell, and white blood and epithelial cell excretion are expressed always as twelve hour rates. The rate of protein excretion per 12 hours is determined by a method developed in this laboratory by Shevky and Stafford[18] and subsequently modified in several respects. It depends on the volume of protein precipitated by a solution of phosphotungstic acid in strongly acidified alcohol, after packing under constant conditions by centrifugalizing. The relation between volume of precipitate and protein concentration was found by Kjeldahl determinations.

These methods are all quantitative but the magnitude of their errors varies widely. The determinations of the rates of urea excretion in the urine and the blood urea concentrations require a high degree of accuracy since they are used for the calculation of the ratio between urine rate and blood concentration, and errors in different directions in the numerator and denominator would result in a gross error in the ratio value. The many possible errors in the urease method for urea determinations have been the subject of continuous study in this laboratory for the past fifteen years. The actual methods used are specially adapted for this sort of work.[19] But the urease method is particularly dangerous from an analytical point of view since it rests on the activity of an enzyme whose mode of action is still unknown. Even the structural formula for urea is not yet decided, so that the whole procedure is empirical and requires most anxious study and continual checking. Although we had every reason to be satisfied that our technic entailed no very appreciable error, there remained always certain perplexities which grew from studies in which the different factors were varied. These difficulties received a somewhat disquieting probable explanation when we found that urease contained arginine, that human red blood cells contained arginase, and that therefore in a mixture of blood and urease part of the urea is derived from the arginine of the urease and is not present in the blood at all.[20] Fortunately throughout this study we had taken pains to keep the proportion of urease and blood constant so that the error from this source tended to be constant except for such variation in arginase as probably occurs in different bloods. The error under the conditions we used is in any case a small one and is always a plus error, but if the urease had been added in variable amount, as often happens, the error might have been considerable. We avoid the error now by using heparin plasma.

For clinical purposes no such painful accuracy is required in the determinations of the rate of protein excretion because the quantities found vary from 10 mg. to 20,000 mg. per twelve hours. The original method had an average error of ±6 per cent and this may have been somewhat reduced by the modifications we have introduced. But any method which measures urinary proteins by volume is occasionally liable to considerable error and for this reason we are attempting now to develop a gravimetric method which will not be too laborious and which will be entirely trustworthy within certain much more narrow limits.

The cast and cell methods are also quantitative but only to a somewhat charitable view. Since such a small sample of the total urine volume is actually counted it is essential always to take care to mix the whole urine thoroughly and also the sediment from the 10 c.c. sample. If this is done it is somewhat surprising how closely counts by different observers usually check. It is, however, absurd to try to make the method quantitative in the strict sense of the word, since it is quite unnecessary. At least for clinical purposes we want to know the rates in terms of orders of magnitude. It is immaterial whether the urine contains one million or one million one hundred thousand casts, although it is essential to be certain whether there are thousands, tens of thousands, hundreds of thousands or millions.

It is perhaps unnecessary to say that these methods have been developed as tools for clinical investigation and that they were never intended for "routine" clinical work. At the present time "routine" work means work done by someone else than the clinician, someone who has no knowledge of the patient or of the purposes for which the work is being done. The necessary degree of accuracy in the timing of urine and blood collections and the constant watchful care in the manipulations of the chemical work can come only from someone who has an immediate personal interest in the results. The cast counting and the counting of the white blood cells and epithelial cells it is true are extremely simple and no doubt technical assistants might give usable results, but the really important matter is the enumeration of the red blood cells and this is a matter for judgment and experience. During the various sudden changes in salt concentration and H-ion concentration to which red blood cells are subjected in their passage from the glomerulus to the bladder, red blood cells assume many curious and bizarre forms. They are usually almost entirely lyzed so that what is to be counted is the shadows of red cells, and these shadows swell and crinkle and have to be differentiated from some crystal forms, from fat droplets and from yeast cells. These various shapes and sizes have to be learned by following cases of hemorrhagic Bright's disease from the initial stage with gross hematuria. As these patients pass into the latent or active stage the red cells may be followed and still recognized through all their changing forms. But without such special experience and without a personal interest in the patient it is scarcely to be expected that reliable results will be obtained. In any case the clinician who is seriously interested in Bright's disease will not permit this work to be delegated to anyone else. It is the direct road to a knowledge of the renal lesion and it would be no more absurd for the heart specialist to employ someone to examine the precordium than for such a man to allow a "routine laboratory" to report on urinary sediments. For there is more in these examinations than can be expressed in figures. It is the picture as a whole which is suggestive, not the separate items, but the suggestion comes only to the man who knows the patient.

Chapter III

CLINICAL DEFINITIONS

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CLINICAL DEFINITIONS*

Most of the terms employed in clinical investigation are the terms of physics and of chemistry, but when they are used by clinicians they transcend the abstract generalized connotation to which they are restricted in the "exact" sciences. Without losing exactitude they gain in significance by becoming elements in the description of a connected series of events. The clinical terms used in this monograph are relatively simple because the object is a simple one, but even they have a significance only in relation to the organized regulations of the body. When we speak of volumes or pressures observed in patients even the immediate meaning is dependent on a conception of the range of volumes or of pressures found in healthy human beings. The figures appeal implicitly to a detailed background of biological knowledge and experience. Their medical meaning will be clear in proportion as the biological knowledge is clear. It is within the province of medicine that this biological knowledge should be acquired, because no general formula will suffice, but only a documented account of measures on normal individuals carried out under exactly those conditions which are subsequently to be used in the clinical investigation. The choice of conditions is all-important. The more precise they are, the more precise will be the deductions which may be drawn; the better adapted they are to the specific requirements of the clinical problem, the more fruitful will be the investigation; for in this field the clinical problem comes first and the necessary biological data are gathered for the sake of the problem and under the particular conditions dictated by its interests.

The "constants" which are the tools of physics do not exist in biology and medicine. Here there is only one constant, the unity of the organism, and all other biological values vary in order that it may remain the same. But when we take pains to maintain as great a degree of constancy in the environment of the organism as is possible, we find that such physical or chemical measurements as, for instance, blood pressure determinations or blood urea concentrations are confined within a certain range of values and that in respect to the frequency with which any given value within this range is observed they will group themselves in accordance with the "normal curve." There is, then, no normal blood pressure or normal blood urea concentration. These are meaningless terms. But for each specified set of conditions there is a certain series of blood pressures and blood urea concentrations which we shall find in individuals free from obvious disease. Each of these ranges will center round an average and the further we go above or below this value the fewer instances we shall encounter until we reach levels where our chances of finding any normal individual who manifests such unusual values will be extremely remote. Thus such a clinical term as the blood pressure of a patient requires for its definition the description of the conditions under which the observation was made, the average value observed in a series of normal individuals, and a statement of the degree to which the measurements deviate above and below it. The measure of this variability is often given by the probable error, a ± quantity which when added to the average will include approximately half of all the values encountered. But for clinical purposes it is often better to express variability as the chance which exists that the particular measurement made in the patient might be found in a healthy individual.

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*T. A.

URINE VOLUME

There is a very great variability in urine volume, because it is largely by means of changes in urine volume that the water content of the blood is regulated. On this account such clinical terms as oliguria, polyuria and nycturia only have significance in cases where the urine volumes are entirely unusual, unless indeed the conditions under which the measurements are made are clearly defined and conform to certain necessary requirements. The essence of the matter is that the conditions be of an extreme character. Unless the body is either depleted of water or flooded with water the volume of urine is too variable to be a sign of any clinical value. Except under such circumstances it varies with all the many unknown and unpredictable factors which determine the water content of the blood, internal and uncontrollable variations to which the kidney is highly sensitive. When, however, we deprive a person of fluids for some time or get him to drink very large volumes of water, we know what to expect; for we have subjected the kidney to known and measurable conditions which call for the exercise of its regulatory function. If under such circumstances we find a large volume in spite of fluid restriction, or a small volume in spite of water drinking, the measurements have an exaggerated difference from those observed in normal individuals and deviate so widely from the normal averages that their meaning cannot be questioned.

In the "dilution and concentration tests" used so widely in Europe the subject is first given fluids and then the degree to which the urine volumes fall after a certain time of abstention from fluid is noted. But no adequate test of the reduction of urine volumes can be obtained in any reasonable time after having thus filled all the water reservoirs of the body. It seemed better, therefore, first to deplete the subject and later to flood him with water. It is an easy matter to introduce large amounts of water quickly into the body, but it takes much longer to free it from all excess.

Urine Volumes after Abstention from Fluids. The subjects took no fluids of any sort from after breakfast on one day until the following morning. They were also required to abstain from any unusual consumption of foods with a high water content. The urine voided between 6 p.m. and

6 A.M. was collected. These are the conditions required for the collection of urine for cast and cell counts. The average volume for these twelve hours of the night was 381 c.c. with a standard deviation of ±113 c.c., and a coefficient of variability of 29.5 per cent. These figures are derived from 94 measurements on 75 normal adults. A statistical definition of the terms "oliguria" and "polyuria" under these particular conditions is given in Table II.

TABLE II

DEFINITION OF OLIGURIA AND POLYURIA

Conditions: Restriction of water intake, twelve-hour night collection

Definition	*Volume of Night Urine Twelve Hours (c.c.)*	*Odds*
Oliguria	21 or less	One normal in 1450
	32 or less	One normal in 1030
	43 or less	One normal in 741
	55 or less	One normal in 527
Doubtful	66 or less	One normal in 385
	77 or less	One normal in 286
	88 or less	One normal in 213
	100 or less	One normal in 162
	111 or less	One normal in 122
	122 or less	One normal in 93
	133 or less	One normal in 72
	144 or less	One normal in 56
Normal	381 or less	One normal in 2
Doubtful	617 or more	One normal in 56
	628 or more	One normal in 72
	640 or more	One normal in 93
	651 or more	One normal in 122
	662 or more	One normal in 162
	673 or more	One normal in 213
	684 or more	One normal in 286
	696 or more	One normal in 385
Polyuria	707 or more	One normal in 527
	718 or more	One normal in 741
	730 or more	One normal in 1030
	741 or more	One normal in 1450

Urine Volumes after Water Drinking. Immediately after the collection of the night urine following the day's abstention from fluid 1000 c.c. of water and 30 gm. of urea were taken. This was at 6 A.M. Every hour thereafter up to and including 11 A.M., 500 c.c. of water were drunk. Hourly collections of urine were made at 10 A.M., 11 A.M., and 12 noon; the largest of these three volumes was taken as the measurement to be used and was multiplied by 12 in order to make it comparable with the volumes obtained after abstention from water. The conditions in this case are those required

Table III

Definition of Oliguria and Polyuria

Conditions: Large water intake, urea administration, hourly collections at height of diuresis

Definition	12 *Hrs. Volume (c.c.)*	*Odds*
Oliguria	4,332 or less	One normal in 1,450
	4,440 or less	One normal in 1,030
	4,548 or less	One normal in 741
	4,656 or less	One normal in 527
Doubtful	4,784 or less	One normal in 385
	4,860 or less	One normal in 286
	4,968 or less	One normal in 213
	5,076 or less	One normal in 162
	5,174 or less	One normal in 122
	5,282 or less	One normal in 93
	5,388 or less	One normal in 72
	5,496 or less	One normal in 56
Normal	7,716 or less	One normal in 2
Doubtful	9,936 or more	One normal in 56
	10,044 or more	One normal in 72
	10,135 or more	One normal in 93
	10,248 or more	One normal in 122
	10,356 or more	One normal in 162
	10,452 or more	One normal in 213
	10,562 or more	One normal in 286
	10,658 or more	One normal in 385
Polyuria	10,776 or more	One normal in 527
	10,884 or more	One normal in 741
	10,992 or more	One normal in 1,030
	11,100 or more	One normal in 1,450

for the measurement of the amount of functioning kidney tissue. The average of 35 measurements on 24 normal adults was 7716 c.c. per twelve hours, the standard deviation was ±1056 c.c. and the coefficient of variability 12.7 per cent.

Volume Quotient. In normal individuals the twelve hours' urine volume changes from 381 c.c. when fluids are restricted to 7716 c.c. when large amounts of water are taken, that is to say the urine volume increases $^{7716}/_{381}$ or more than 20 times. This quotient measures the range of adaptation of the kidney to these two diverse conditions. But of course the conditions are not of such a nature as to exclude all factors other than the kidney. On the contrary the high variability of both measurements is due mainly to uncontrolled variation in extrarenal factors. When we pass from normal individuals to patients we find that these extrarenal sources of variation may become factors of major importance which give rise to clear abnormalities in urine volume in relation to the normal standards. Thus we have observed in patients with edema who are in process of unloading retained fluid that the volumes of urine obtained after abstention from fluid are abnormally large. Under these conditions there is polyuria. When large amounts of fluid are given there is also a tendency towards polyuria, so that the volume quotient is not greatly altered. Similarly when a patient is becoming edematous the urine volumes are low both after fluid restriction and after water administration, and again the value of the quotient is not greatly affected. So, also, other extrarenal factors influence both tests towards either oliguria or polyuria. It is altogether different when the quantity of functioning renal tissue is greatly reduced. We then see a divergence in the direction of the abnormalities. There is polyuria when the fluids are restricted and oliguria when water is taken. There is, therefore, a very striking decrease in the value of the volume quotient, a decrease which is a measure of the reduction in the range through which the kidney is able to adapt itself to variations in its environment. On this account there is a greater correlation between changes in the volume quotient and the amount of functioning renal tissues than can be found for either polyuria after fluid restriction or oliguria after water consumption. The degree of correlation, which naturally is not pronounced, is shown in Figure 4. The statistical definition is given in Table IV. The average quotient is 20.2 with a standard deviation of ±6.08 and a variability of ±30.2 per cent.[21]

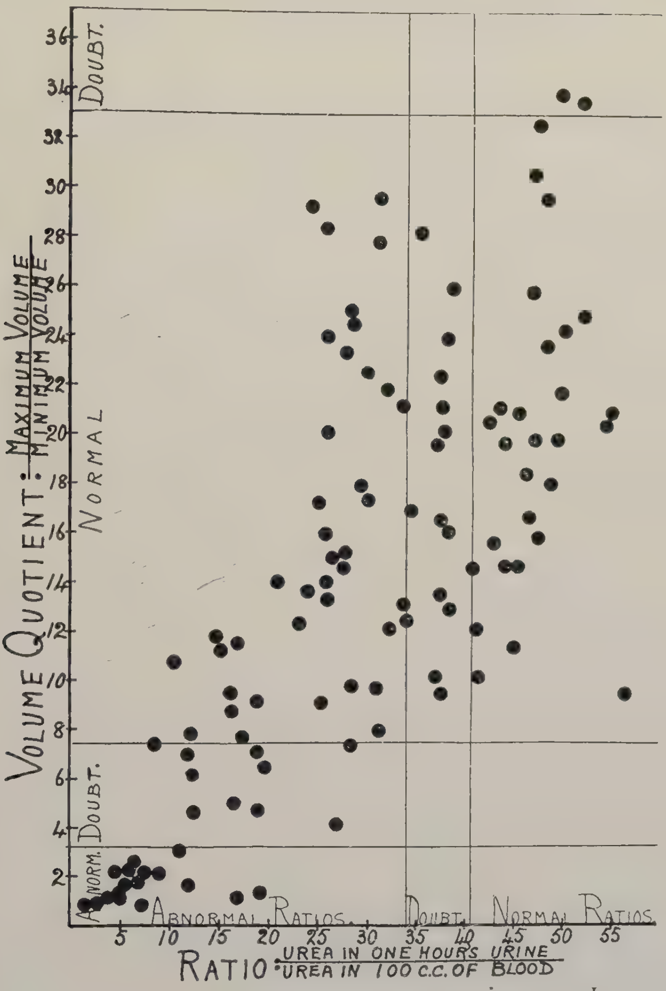

Fig. 4. Relation between volume quotient, i.e., $\frac{\text{maximum volume}}{\text{minimum volume}}$ and amount of secreting tissue in kidney.

Table IV

Definition of Relation between Maximum and Minimum Urine Volumes

Number of times by which the maximum volume exceeds the minimum volume

Definition	*Maximum Volume* *Minimum Volume*	*Odds*
Abnormally low	0.75 or less	One normal in 1450
	1.4 or less	One normal in 1030
	2.0 or less	One normal in 741
	2.6 or less	One normal in 527
Doubtful	3.2 or less	One normal in 385
	3.8 or less	One normal in 286
	4.4 or less	One normal in 213
	5.0 or less	One normal in 162
	5.6 or less	One normal in 122
	6.2 or less	One normal in 93
	6.8 or less	One normal in 72
	7.4 or less	One normal in 56
Normal	20.2 or less	One normal in 2
Doubtful	33.0 or more	One normal in 56
	33.6 or more	One normal in 72
	34.2 or more	One normal in 93
	34.8 or more	One normal in 122
	35.4 or more	One normal in 162
	36.0 or more	One normal in 213
	36.6 or more	One normal in 286
	37.2 or more	One normal in 385
Abnormally high	37.9 or more	One normal in 527
	38.4 or more	One normal in 741
	39.1 or more	One normal in 1030
	39.7 or more	One normal in 1450

Specific Gravity of the Urine

There could scarcely be any term which would more sharply differentiate the physicist from the medical man than the phrase "specific gravity of the urine." To the clinician it brings to mind a measurement of long proved usefulness. To the physicist there can be nothing "specific" about the weights of equal volumes of fluids which contain many substances in varying and unknown concentration. Each of these substances has a specific effect on the weight. Sodium acid phosphate, for instance, increases the weight of a solution relatively to an equal volume of water more than the same quantity of sodium chloride and much more than the same quantity of urea. Therefore in urine which contains these and many other substances the "specific gravity" is dependent on the varying relative proportions of all the urinary constituents and so their combined weight cannot be deduced from this measurement.[22] How widely the specific gravities of equal concentrations of sodium acid phosphate, sodium chloride and urea differ from one another is shown in Figure 5.

But to the clinician the urine is not simply a solution containing unknown concentrations of various chemical substances. Within limits, wide indeed but measurable, it has a constancy of its own since it is derived from the controlled internal medium of a living body in which there is ordinarily no very great departure from a certain pattern of proportions between the concentrations of its constituents, and he has learned to note the variations in the specific gravity of the urine as an empirical means towards an understanding of one of the methods by which the inner constancy of the organism is maintained. And so in spite of the ambiguity which clouds its physical interpretation the specific gravity of the urine is still a term which has not lost all meaning in medicine. But it is, of course, all the more important to get rid of the impression, which still lingers in the textbooks, that the specific gravity is a measure of the concentration of total solids in the urine.

In Germany, Hedinger and Schlayer[23] introduced the idea of making observations in consecutive urine collections over a period of twenty-four hours under certain dietary conditions. In this country the same plan has been followed though usually without any requirement of special conditions. Under the variations induced by the usual food and fluid intake the body

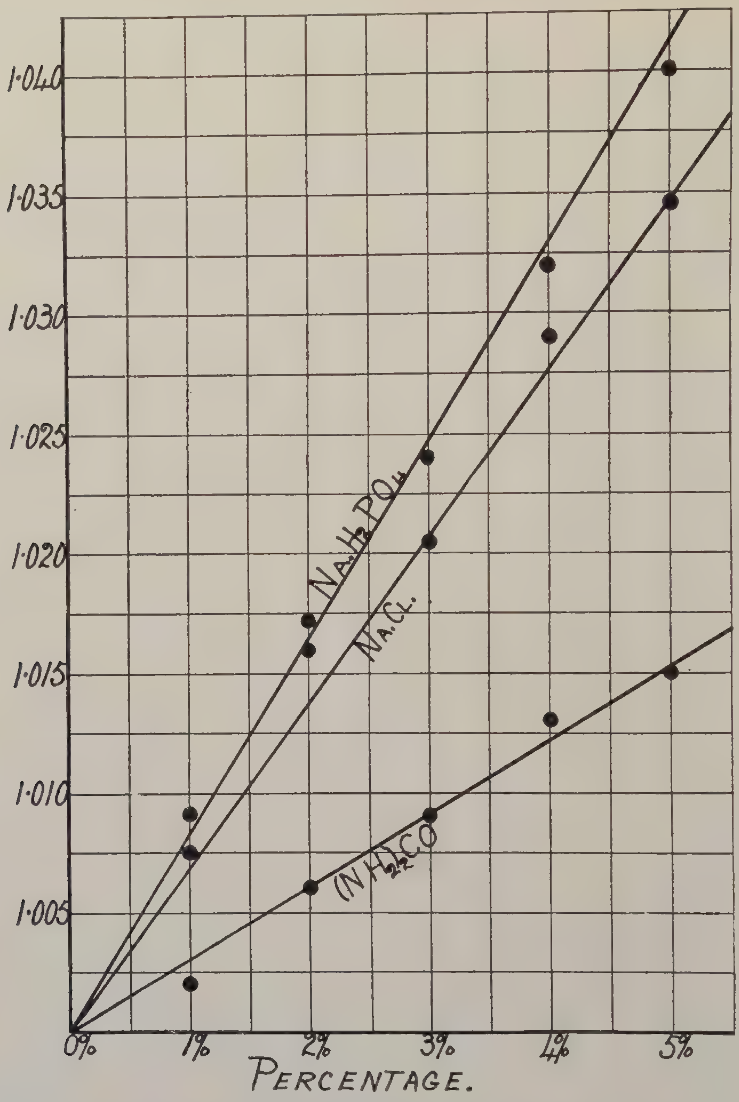

FIG. 5. Specific gravity of varying concentrations of urea, sodium chloride and sodium acid phosphate. Figure shows wide differences between specific gravities of equal concentrations of these substances. Thus 3 per cent concentrations of urea, sodium chloride and sodium acid phosphate have specific gravities of approximately 1.009, 1.020, and 1.024.

reacts by varying the rate of excretion of water and of the various other urinary constituents so that considerable differences usually arise in the specific gravity of the series of urine collections. This variability is the sign of health. When it is absent it is proper to suspect that there may be a defect in the regulatory processes of the body.

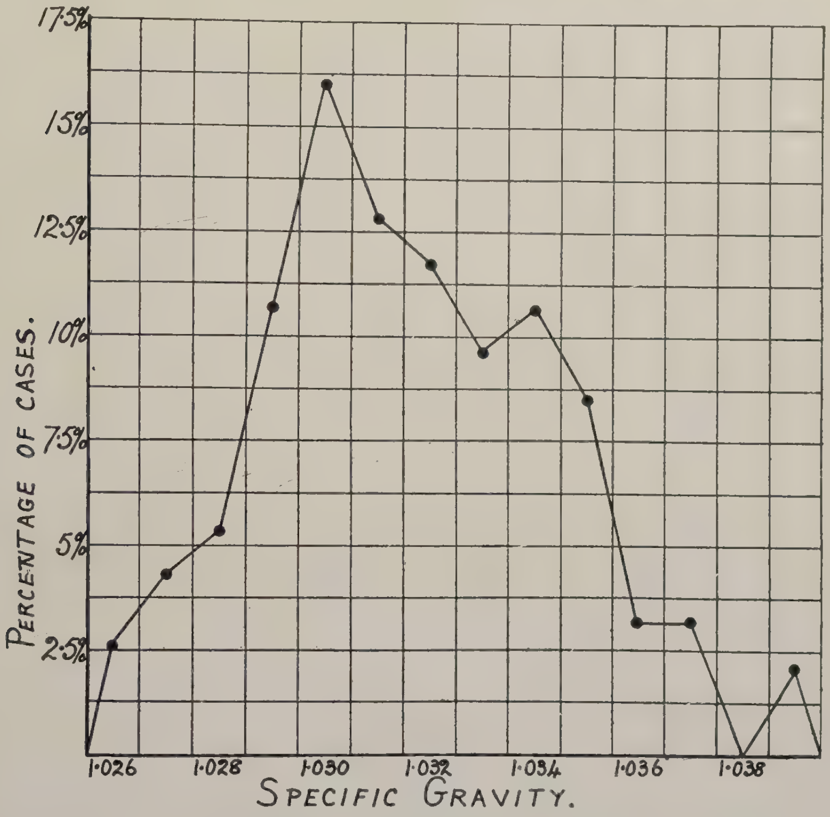

Fig. 6. Percentage frequency distribution of specific gravity of night urine in normal individuals after restriction of fluids.

The conditions observed in the foregoing test conform to those of ordinary life, and while this renders it widely applicable, it also robs it of any precise meaning except when an extremely constant low level of specific gravity values is encountered. Under more rigorous conditions the term might come to have a more definite significance. We can produce the conditions under which the urine usually has a high or a low specific gravity in two ways, either by varying the ingestion of solid matter or of water. In practice it is better to vary the water intake, mainly because if any particular solid is given the effect will depend on its own individual specific gravity effect in combination with that of the residual mixture, whereas if the usual balance of urinary constituents is left undisturbed the specific gravity has within certain rather wide limits a mean value which may be altered directly by changes in the rate of water excretion.

High Specific Gravities. The same conditions were imposed as in the measurement of low urine volumes, that is to say the subject took no fluids after breakfast on one day until the morning of the next day and collected the twelve hours' night urine. The frequency distribution of 94 observations on 75 apparently healthy individuals is given in Figure 6.

The average specific gravity is 1.032 (a much higher value than is met under ordinary conditions). The standard deviation is ±0.0028 and the coefficient of variability 8.8 per cent.

Table v gives the odds that the urine of any normal individual under these conditions would have as low or a lower specific gravity than the values given in Column 1.

TABLE V

ODDS THAT ANY NORMAL INDIVIDUAL UNDER CONDITIONS OF TEST WOULD GIVE AS LOW OR A LOWER SPECIFIC GRAVITY THAN THOSE GIVEN BELOW

Specific Gravity	*Odds*
1.026	1 normal in 47
1.025	1 normal in 115
1.024	1 normal in 323
1.023	1 normal in 1000
1.022	1 normal in 5000

These figures seem to promise a fairly sharp differentiation between health and disease, but in actual practice the test is often inapplicable because one of the implicit conditions, the consumption of the usual amount and variety of food, is not complied with. Most of our patients were on a low salt diet, and the effect of a reduction in sodium chloride intake is pronounced. Five normal individuals, whose average specific gravity had been 1.032 under the usual conditions, had an average of 1.027 after they had lived on a low salt, low protein diet and had a range of variation of from 1.019 to 1.033.[24]

The significance of specific gravity determinations could undoubtedly be extended by observations on normal individuals kept under the same dietary conditions as are usual for patients, and particularly by observations made on normals after the ingestion of large amounts of water. It is the quotient derived from the division of the high specific gravities by the low specific gravities which would most sharply reveal any failure of accommodation to changes in the environment. Such observations might have some general medical interest. But from the point of view of the kidney, which is our immediate interest, there is no doubt that it is more accurate, if less easy, to deal with concentrations of one substance and thus be freed from the uncertainties necessarily involved in such a complex term as the specific gravity of the urine.

Blood Urea Concentration

In 1927, E. M. MacKay and L. L. MacKay[25] published the frequency distribution of 278 blood urea concentrations observed in normal individuals. This is given in Figure 7, page 54.

The mean value was 29.3 mg. urea per 100 c.c. The extreme range was from 11 mg. to 48 mg. per 100 c.c., the standard deviation ±6.98 and the coefficient of variability 4.01 per cent.

The range of normal variation is greater for urea than for any other normal constituent of the urine found in the blood and it is important for clinical reasons that its limits should be thus clearly defined. But it should be noted that these limits refer to the determination of urea in whole blood by the urease method, and that it is possible that the variability would be narrowed by the use of methods under which there is no chance of urea formation from arginine.[20] This possibility is at present under investigation, but in any case the revelation of this wide fluctuation in normal blood urea values as observed by the method which still is the usual clinical procedure makes it impossible to attach any final significance to blood urea concentrations of between 40 and 50 mg. when they are met in patients. Still greater reserve is necessary in the interpretation of a high blood urea concentration as an indication of any renal abnormality. A concentration of over 100 mg. per 100 c.c. may be obtained at will in any individual with normal kidneys in full activity simply by feeding urea. There are many clinical conditions in which a marked increase in endogenous urea formation

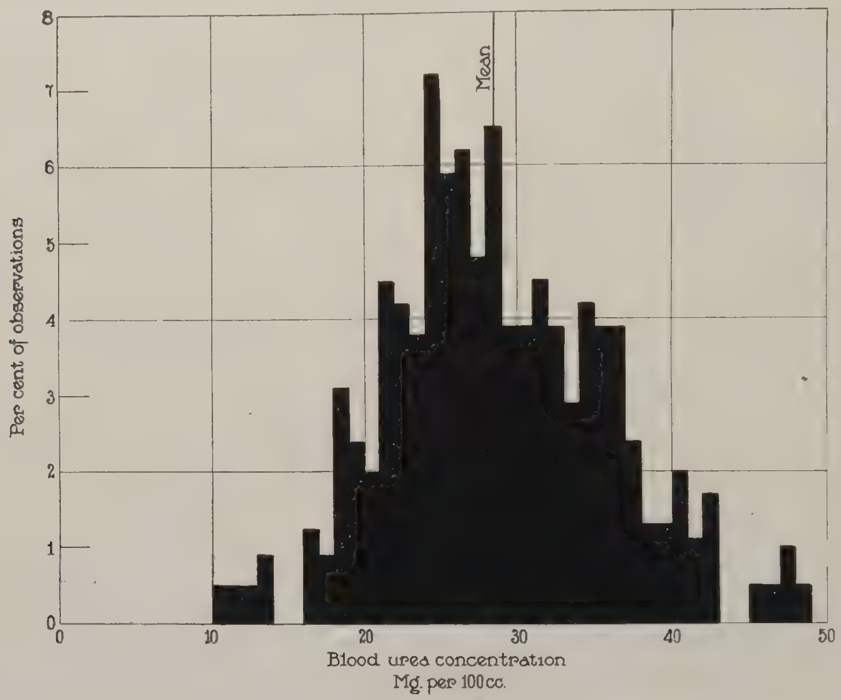

FIG. 7. Distribution of 278 (220 males and 58 females) observations.

coincides with renal inactivity and in all such cases blood urea concentrations up to 100 mg. may occur without any decrease in the potential amount of actively functioning renal tissue. L. L. MacKay and E. M. MacKay produced an average level of 184 mg. per 100 c.c. in rabbits simply by depriving them of food and water for 100 hours.[26] The meaning of a blood urea concentration in any individual patient is thus dependent on the clinical conditions and is not a matter to be judged solely by reference to a table of normal values. But wherever a toxic destruction of body protein and states of renal inactivity can be excluded the significance rests only on the demarcated limits of variation in normal individuals.

RELATION BETWEEN THE BLOOD UREA CONCENTRATION AND THE AMOUNT OF FUNCTIONING RENAL TISSUE. When the blood urea concentration is measured in patients with Bright's disease under conditions which are the same as those obtaining in normal individuals, the values observed bear a certain rough relationship to the amount of functioning renal tissue which they still possess. E. M. MacKay and L. L. MacKay[17] have shown the nature of this relationship in Figure 8, in which the blood urea concentrations have been plotted against the percentage of normal functioning renal tissue as measured by the ratio, rate of urea excretion ÷ blood urea concentration.

As the amount of renal tissue decreases there is a slight increase in the average blood urea concentration but it is so slight that it is not until less than 40 per cent of the usual amount of renal tissue remains that the average reaches the upper limit of normal variation for blood urea concentration. Thereafter the blood urea values rise higher and higher as the amount of functioning tissue is still further reduced. The average relationship is given in Table VI.

In considering these facts it should be remembered that the measurements of renal tissue were made while the kidney was in full activity, whereas the corresponding blood urea concentrations were determined under the

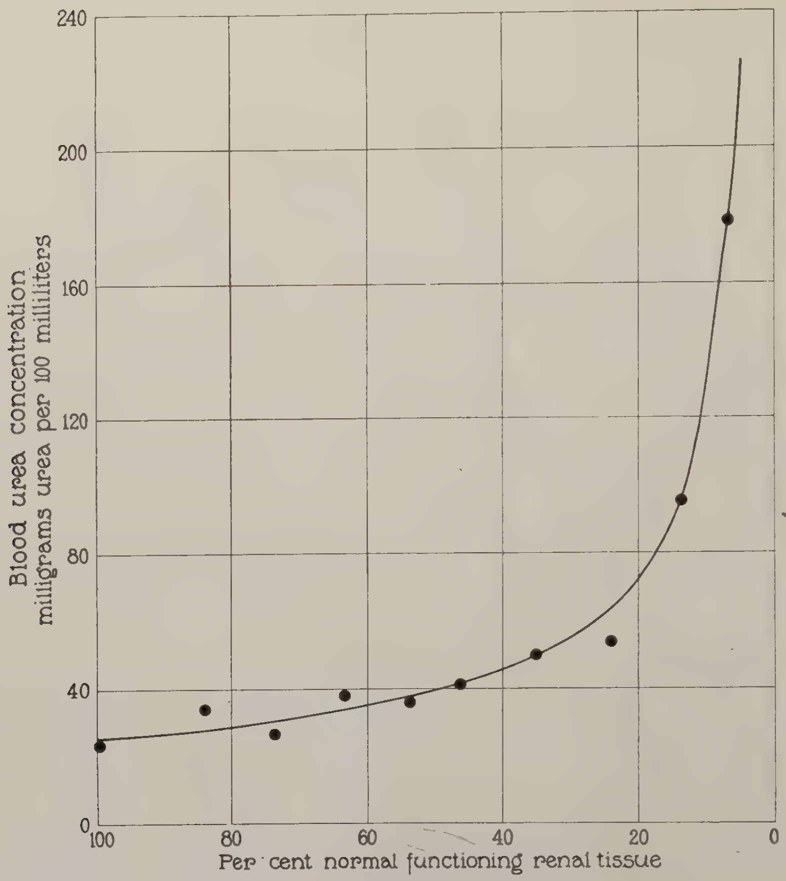

FIG. 8.

TABLE VI

Average Blood Urea Concentration (*mg. per* 100 *c.c.*)	*Amount of Renal Tissue* (*per cent of normal*)
27	99
35	83
29	74
38	63
36	54
51	46
50	35
55	24
95	14
179	6

ordinary conditions of every-day life. Under the latter conditions it is the degree of activity at the time of observation, not the potential activity of the kidney as limited by its size which enters into the regulation of the blood urea concentration. It may very well be that as the amount of renal tissue decreases what is left tends more constantly to have a great proportion of its glomeruli flushed with blood, so that even when half the renal tissue has been destroyed the level of blood urea concentration is maintained within normal limits. In any case it is a striking fact that in this series more than two-thirds of the patients whose kidneys were only 40 to 60 per cent of the normal size had blood urea concentrations below 40 mg. per 100 c.c.

When the quantity of renal tissue becomes less than 40 per cent of the normal these compensatory processes begin to fail and the blood urea concentration for a time increases in proportion as the amount of kidney decreases. It is here and here only that successive blood urea determinations in individual patients come for a time to possess an anatomical significance. It is possible to translate the gradual increase in blood urea concentration into terms of renal tissue by means of the average relation between these two values given in Table VI. The fairly close agreement which may be thus obtained is shown in Figure 21, p. (349). These observations were made on one of the series of cases whose course will be subsequently described. The rate at which the kidney decreased in size is shown by the solid dots, while the predictions derived from the blood urea concentration values are charted as circles.

At the very end as the patient passes into true uremia there is again no usable correlation between blood urea concentration and quantity of renal tissue, because now the patient is in a toxic state in which the actual level of blood urea concentration is greatly influenced by the variable rate of production of endogenous urea.

Blood Pressure

The blood pressure and pulse rates of soldiers between twenty-one and thirty-one years of age were measured under three sets of conditions. First, the readings were made in the early morning before they had risen from bed. These were called basal conditions.[27] Second, measurements were made under what are called daytime conditions by which it is understood that the subjects had had food but had undergone only the ordinary exertions of a sedentary life. Thirdly, the pressures and pulse rates were obtained after the men had hopped 100 times in time with a metronome striking at a rate of 120 to the minute. These are termed exercise conditions. In addition a small group of individuals were observed after heavy exercise. This consisted in hopping 100, 200, 300, 400 and 500 times, with 180 second intervals of rest between each series of hops. Under all these conditions of rest or activity the men were lying down while the measurements were being made. Three hundred individuals were examined under daytime and exercise conditions, 76 for basal conditions and 5 after heavy exercise. The average results are given in Table vii.

Table vii

Conditions	Systolic	Diastolic	Pulse pressure	Pulse rate	P.P. × P.R.
Basal	99	71	28	63	1,764
Daytime	129	78	50	80	3,980
Exercise	156	68	88	101	9,030
Heavy exercise	162	51	111	118	13,160

These figures show that the definition of "normality" in blood pressure requires first of all an exact delimitation of the conditions under which the observations are to be made. But they show more than this. The increase in systolic pressure from 127 under daytime conditions to 156 after moderate and 162 after heavy exercise is primarily a cardiac manifestation, for it may be ascribed mainly to the increased quantity of blood forced into the aorta by the heart at each systole. The decrease in diastolic pressure from 78 to 68 to 51 under the same three states is due to a diminution in the degree of constriction of the arterioles. It is a peripheral vascular manifestation. The pulse pressure increase from 50 to 88 to 111 is a more complete indication of the nature of the circulatory change, for it is the result of the combined effect of the increased activity of the heart and the decreased tonus of the arterioles and is an indication of the total amount of blood supplied to the body with each beat of the heart. But the pulse rate increases from 80 to 101 to 118 and if we take the product of the pulse rate and the pulse pressure we obtain the most complete measure of all, one which gives us a clinical means of judging the direction and extent of changes in the rate of flow of blood per unit of time.

Each of these measures alters with alteration in the conditions, but each changes in unison and in proportion to the other, so that if we regard them not in isolation but as parts of a whole we perceive the significance of such partial deflections from the usual as we are accustomed to see in patients. For during life the cardiovascular system never far fails in its work of supplying the organism with that amount of blood which its changing state requires. As one or other of the means for the fulfillment of this end is encroached on by disease the remaining factors are brought into fuller play. It is by the observation of a deviation from the usual balance of the individual factors that the location and nature of disease may sometimes be detected. If the heart is weak so that it cannot pump much more blood at each stroke, the need for a greater circulation rate will be met by a greater increase in pulse rate and decrease in peripheral resistance. If, through an obstruction in the conducting system, the heart rate cannot be augmented, there will be a compensatory increase in the amount of blood ejected at each stroke, the systolic pressure will rise higher, the diastolic lower and the increase in pulse pressure will alone suffice. If there is an inhibition of the usual arteriolar relaxation the pulse pressure will be increased by a correspondingly greater elevation of the systolic pressure. In spite of all such localized difficulties the cardiovascular system as a whole adjusts itself always to the circulatory requirements of the body.

When patients are in a hospital it is not hard to measure the blood pressure under basal conditions. Table VIII gives the odds against as high or higher values than those stated occurring in normal individuals.

TABLE VIII

BASAL CONDITIONS. ODDS THAT A NORMAL INDIVIDUAL UNDER BASAL CONDITIONS WILL SHOW AS HIGH OR A HIGHER LEVEL OF PRESSURE AND PULSE RATE AS THOSE GIVEN BELOW

Systolic	Odds	Diastolic	Odds	Pulse pressure odds	Odds	Pulse rate	Odds	P.P. × P.R.	Odds
118	1 in 24	88	1 in 25	43	1 in 26	77	1 in 24	2900	1 in 27
119	1 in 29	89	1 in 32	44	1 in 33	78	1 in 31	2950	1 in 33
120	1 in 36	90	1 in 40	45	1 in 44	79	1 in 42	3000	1 in 39
121	1 in 44	91	1 in 51	46	1 in 59	80	1 in 56	3050	1 in 47
122	1 in 55	92	1 in 67	47	1 in 80	81	1 in 76	3100	1 in 58
123	1 in 69	93	1 in 86	48	1 in 106	82	1 in 106	3150	1 in 69
124	1 in 86	94	1 in 112	49	1 in 147	83	1 in 147	3200	1 in 84
125	1 in 104	95	1 in 147	50	1 in 208	84	1 in 208	3250	1 in 104
126	1 in 141	96	1 in 204	51	1 in 306	85	1 in 303	3300	1 in 128
127	1 in 182	97	1 in 270	52	1 in 417	86	1 in 435	3350	1 in 161
128	1 in 233	98	1 in 385	53	1 in 625	87	1 in 666	3400	1 in 201
129	1 in 313	99	1 in 526	54	1 in 910	88	1 in 1000	3450	1 in 256
130	1 in 417	100	1 in 770	55	1 in 1430	..	....	3500	1 in 323
131	1 in 555	101	1 in 1000	..	....	..	....	3550	1 in 417
132	1 in 741	...	....	..	....	..	....	3600	1 in 526
133	1 in 1000	...	....	...	....	..	....	3650	1 in 666
								3700	1 in 833
								3750	1 in 1111

The blood pressures cited in connection with the patients described in this monograph were, with very few exceptions, taken under approximately "daytime" conditions and Table IX may be used in the interpretation of their significance.

TABLE IX

DAYTIME CONDITIONS. ODDS THAT A NORMAL INDIVIDUAL UNDER DAYTIME CONDITIONS WILL SHOW AS HIGH OR A HIGHER LEVEL OF PRESSURE OR PULSE RATE AS THOSE GIVEN BELOW

Systolic	Odds	Diastolic	Odds	Pulse pressure	Odds	Pulse rate	Odds	P.P. × P.R.	Odds
160	1 in 23	97	1 in 23	74	1 in 24	102	1 in 27	6799	1 in 26
161	1 in 26	98	1 in 29	75	1 in 29	103	1 in 32	6800	1 in 29
162	1 in 29	99	1 in 34	76	1 in 33	104	1 in 38	6900	1 in 33
163	1 in 33	100	1 in 42	77	1 in 40	105	1 in 47	7000	1 in 39
164	1 in 38	101	1 in 52	78	1 in 47	106	1 in 55	7100	1 in 45
165	1 in 44	102	1 in 65	79	1 in 56	107	1 in 69	7200	1 in 53
166	1 in 51	103	1 in 82	80	1 in 67	108	1 in 84	7300	1 in 62
167	1 in 58	104	1 in 104	81	1 in 80	109	1 in 101	7400	1 in 74
168	1 in 69	105	1 in 133	82	1 in 98	110	1 in 128	7500	1 in 86
169	1 in 78	106	1 in 170	83	1 in 119	111	1 in 161	7600	1 in 104
170	1 in 91	107	1 in 222	84	1 in 145	112	1 in 204	7700	1 in 122
171	1 in 106	108	1 in 286	85	1 in 182	113	1 in 250	7800	1 in 147
172	1 in 125	109	1 in 385	86	1 in 222	114	1 in 323	7900	1 in 175
173	1 in 147	110	1 in 500	87	1 in 270	115	1 in 416	8000	1 in 208
174	1 in 175	111	1 in 666	88	1 in 333	116	1 in 526	8100	1 in 256
175	1 in 207	112	1 in 910	89	1 in 417	117	1 in 714	8200	1 in 303
176	1 in 250	113	1 in 1250	90	1 in 526	118	1 in 910	8300	1 in 385
177	1 in 294	...	....	91	1 in 666	119	1 in 1250	8400	1 in 455
178	1 in 345	...	....	92	1 in 834	...	....	8500	1 in 588
179	1 in 417	...	....	93	1 in 1111	...	....	8600	1 in 714
180	1 in 500	...	....	..	....	...	....	8700	1 in 833
181	1 in 625	...	....	..	....	...	....	8800	1 in 1111
182	1 in 740								
183	1 in 909								
184	1 in 1111								

None of the standards we have given conform to ideal requirements in respect to the conditions under which the observations were made.

The normal adult measurements were made with a view to a special clinical purpose for which they sufficed.[28] They included standards for the reactions to exercise and so fulfilled the requirement that measurements should be

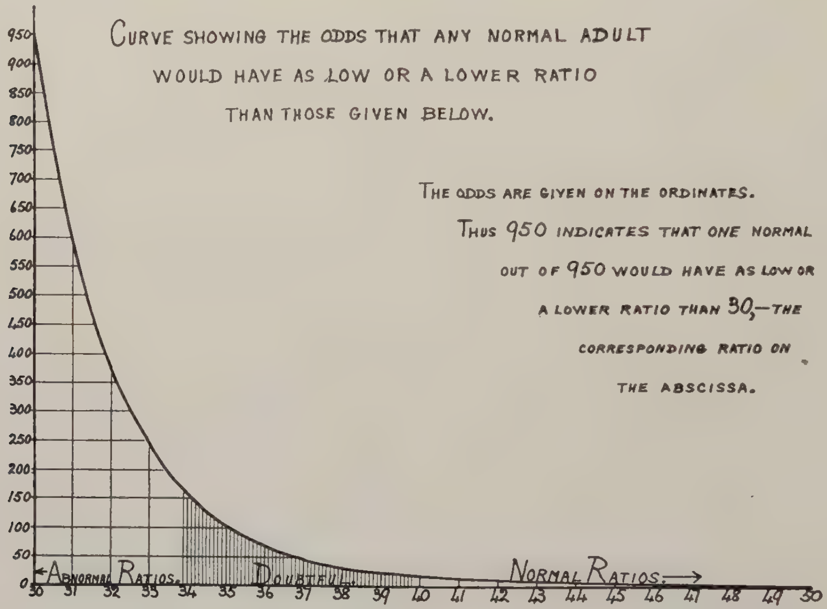

FIG. 9. Provisional separation of ratios obtained in adult men or women into those which can be regarded as within limits of normal variation (normal ratios), those which are regarded as beyond these limits (abnormal ratios), and those which cannot with any certainty be described as either normal or abnormal (doubtful ratios).

made under strain, but such tests are not uniformly applicable to patients with Bright's disease. And in Bright's disease the particular factor which is most often defective is the relaxation at need of the peripheral arterioles. There is a great need for a test which will be particularly designed towards this end. In the meantime the diastolic pressure standards under basal or daytime conditions afford a more certain means for the detection of the special circulatory difficulties seen in Bright's disease than do the systolic pressure standards, for this factor is less susceptible to accidental variations.

$$\text{The Ratio: } \frac{\text{Rate of Urea Excretion in One Hour}}{\text{Blood Urea Concentration}}$$

The particular conditions observed for this measurement have already been given in detail under the section on the technic of the clinical methods. Here we are dealing only with the distribution of values observed in normal individuals. In 163 ratios measured in 31 subjects who were in apparent health the average ratio was 50.4 (5040 c.c. of blood freed from urea in one hour). The standard deviation was ±6.6 and the coefficient of variability 13.1 per cent. Figure 9 and Table x illustrate the chances for any given value occurring in normal individuals.

Table x

Odds That Any Normal Person Will Have as Low or a Lower Ratio Than Those Given in the Table

Ratio	*Odds*	
50.4 or less	1 in 2	Normal
40.5 or less	1 in 15	
39.8 or less	1 in 18	Doubtful
39.2	1 in 22	
38.5	1 in 28	
37.9	1 in 35	
37.2	1 in 44	
36.5	1 in 56	
35.9	1 in 72	
35.2	1 in 93	
34.5	1 in 122	
33.9 or less	1 in 162	Abnormal
33.2	1 in 213	
32.6	1 in 286	
31.9	1 in 385	
31.2	1 in 527	
30.6	1 in 741	
27.9	1 in 1630	

The variability measured here is in part due to differences in the body size of the subjects. This factor would have been diminished if we had cor-

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rected for each subject's body surface as calculated from his height and age. At the time when the measurements were made, however, we did not have the data which later showed that body surface was the measure of body size which varied most closely with the size of the kidney. But the average calculated body surface of the group was 1.82 sq.m. so the average quantity of blood freed from urea in one hour is $\frac{5040}{1.82}$ or 2770 c.c. per square meter per hour. This figure is taken as 100 per cent renal tissue and the quantities found in patients are given as a percentage of this average value.

URINARY SEDIMENT

The conditions have already been given in full. The average number of casts in the twelve hours' urine of normal individuals (medical students) was 1040. The red blood cells average 65,750 and the white blood cells and epithelial cells 322,500 per twelve hours. The individual observations are given in Table XI.

The entire range of measurements has been given here because the series reveals that none of these observations alone has much significance. Thus in 74 subjects casts were found in 45 and are noted as absent in 29. But since only about 1 part in 1000 of the urine was actually inspected it is evident that the absence is the result of the crudity of the method rather than due to an actual absence. This also applies to the cases in which no red blood cells were found. This defect in the method does not exist when it is utilized for counting casts and cells in the urine of patients with Bright's disease, because there the numbers are often in the millions and a considerable degree of accuracy can be attained if that is regarded as desirable for any special purpose.

These figures were obtained from adults all less than thirty years of age, and all free from any obvious disease or infection. It may be that there are many diseases usually not thought of in relation to Bright's disease which

Table XI

Ranges of Variation in the Rates of Excretion per Twelve-hour Night Period of Casts, Red Blood Cells and White and Epithelial Cells in the Urine of Apparently Healthy Men

Casts	Red blood cells	White and epithelial cells
4,270	425,000	1,835,000
4,230	422,000	1,230,000
4,140	417,000	859,000
3,150	353,000	773,000
2,810	276,000	724,000
2,695	270,000	686,000
2,340	237,000	668,000
2,240	208,000	651,000
2,220	194,000	628,000
2,220	187,000	616,000
2,220	181,500	560,000
2,220	162,000	480,000
2,170	159,000	471,000
2,060	145,000	456,000
1,970	118,000	438,000
1,780	104,000	408,000
1,780	74,000	395,000
1,690	73,000	372,000
1,690	70,000	364,000
1,640	69,800	360,000
1,535	63,400	359,000
1,450	56,400	350,000
1,400	53,000	349,000
1,390	45,500	345,000
1,380	38,500	322,200
1,370	32,200	315,000
1,350	29,800	300,000
1,350	26,500	272,000
1,290	26,100	271,000
1,260	22,200	265,000
1,210	19,400	259,000
1,200	16,100	259,000
1,180	10,100	244,000
1,159	9,860	239,000
1,110	5,060	233,000

TABLE XI.—(*Continued*)

Casts	Red blood cells	White and epithelial cells
1,090	3,100	228,000
1,070	0	210,000
1,050	0	206,000
1,050	0	203,000
925	0	202,000
840	0	196,000
704	0	182,000
676	0	174,000
658	0	172,000
645	0	168,000
583	0	165,000
580	0	163,000
556	0	158,000
528	0	157,000
0	0	147,000
0	0	142,000
0	0	139,000
0	0	130,000
0	0	130,000
0	0	129,000
0	0	126,000
0	0	120,000
0	0	119,000
0	0	116,300
0	0	113,400
0	0	111,000
0	0	90,800
0	0	84,000
0	0	80,400
0	0	66,800
0		60,600
0		56,400
0		40,000
0		32,400
0		
0		
0		
0		

produce each of them its own characteristic change inthe urinary sediment. If in such instances the bounds of normal variation are much exceeded they would come under the very broad clinical definition of Bright's disease which we have given.

This section on clinical definitions could be omitted without appreciably diminishing that small residue of fact which may emerge from this study. Certainly in the individual cases we describe the experienced clinician is competent to separate the essential from the non-essential without consulting tables or calculating probabilities, and in any case the immediate problems of medicine are of a qualitative nature and require a sense of proportion much more than a capacity for rigorous thought. So it is not included because of any illusion as to its usefulness but only because it seems worth while at least to try to diminish the looseness and lack of precision of our clinical descriptions by giving the biological background against which the figures representing blood pressures, volumes and specific gravities of urine, blood urea concentrations, rates of cast and cell excretion and ratio measurements acquire such significance as they possess.

CHAPTER IV

A CLINICAL CLASSIFICATION OF BRIGHT'S DISEASE IN ACCORDANCE WITH THE NATURE OF THE RENAL LESION

CHAPTER IV

A CLINICAL CLASSIFICATION OF BRIGHT'S DISEASE IN ACCORDANCE WITH THE NATURE OF THE RENAL LESION*

Every student of Bright's disease constructs his own classification to meet his own individual interests and needs. There was a special interest in the kidney and so this classification began as a classification of the renal lesions in Bright's disease rather than of Bright's disease as a whole. It still remains to be shown to what degree divisions based on the pathology of the kidney alone may suffice to include all the other lesions for only if such a correspondence existed would this classification be of value in prognosis or be founded on true etiological differences. There was also a special need, a purely clinical need, and so the classification is purely clinical. It was the need to answer the question which every patient with albuminuria presents, the question as to what sort of renal lesion exists. We know that some sorts progress relentlessly towards an almost complete destruction of the kidney, that others advance very slowly and gradually, that some last for a little while in great intensity and then vanish and that others, many others, are of no clinical importance at all. But it is always a question of immediate and pressing clinical importance and I think it will be admitted that with our present clinical methods it frequently remains unanswered. So often the history fails to reveal anything of etiological significance, and the physical examination yields negative results. Even such abnormalities as edema or hypertension are notoriously deceptive guides in prognosis. And in this matter tests of renal function are of extraordinarily little value. For the same abnormalities of function are observed in transient lesions as are found in lesions which are lasting, progressive and fatal. This remains true even though the function is observed by those methods and under those conditions which allow one to pass from function to structure, for all that such methods give is the quantity of renal tissue. They tell nothing as to the nature of the lesion which has led to changes in the amount of functioning tissue, and it is the nature of the lesion, not its extent, which determines the patient's fate. The only remaining clinical approach to an answer to this question is the attempt to deduce the nature of the lesion from a study of the morphology of the urine.

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* T. A.

It is best to be clear from the start as to how much at most can be expected from this method. It can never tell us anything about any lesion which has led to the cessation of function of any renal element. Thus, for instance, the clinician can never thus hope to learn about the replacement of functioning tissue by fibrous tissue, the process from which the pathologist has learned so much. He has to be content with forming a judgment as to the nature of the lesion from material derived from those renal elements in which the lesion is still active. This material, further, consists only of the waste products from the active lesion. The proliferation of cells within Bowman's capsule, for instance, will remain hidden. All that will come through into the urine will be the loosened epithelial cells, the leucocytes, the casts, the red blood cells, and the protein that leaks through the damaged glomerular membrane. A cloudy swelling or a fatty degeneration will be revealed only by those tubule cells which happen to die, become detached, and float off in the stream of urine. And to add to all these limitations there is the fact that only the simplest and crudest morphological methods of differentiation can be used, or at least have as yet been used. The cells we see in the urine are for the most part not only dead but already so disintegrated that their original structure can only be surmised. It is not even possible with sufficient certainty to differentiate between a leucocyte and an epithelial cell, because so many are swollen, distorted and divested of their differentiating characteristics. Lastly, there is the ever-present doubt as to the place of origin of any individual cell since the urine drains the whole of the urinary tract. These doubts and difficulties are all warnings against hasty speculation. There seems to be room only for the barest empiricism.

Hemorrhagic Bright's Disease

There is a clinically well-defined group of patients who are observed to develop gross hematuria, a hard edema, and a moderate hypertension during convalescence from some streptococcal disease such as tonsillitis or scarlet fever. It was while watching these patients and while developing methods for the ennumeration of their sediment abnormalities that it was

Table xii

The Initial Stage of a Hemorrhagic Bright's Disease with a Sudden Cardiac Death Early in the Latent Stage

Days from onset	Extent of lesion	Nature and intensity of lesion			
	Functioning tissue	Protein	Casts	Red blood cells	White and epith. cells
	Per cent of normal	Mg. per 12 hrs.	Per 12 hrs.	Per 12 hrs.	Per 12 hrs.
1	(15)	2,400	1,190,000	625,000,000	57,000,000
27	..	610	330,000	675,000,000	59,000,000
32	68	511	390,000	225,000,000	13,000,000
37	..	695	252,000	195,000,000	13,000,000
55	..	324	208,000	176,000,000	5,400,000
96	..	65	33,300	85,000,000	4,700,000
117	..	29	19,100	68,000,000	1,210,000
154	..	12	27,200	40,000,000	1,400,000
155	Died suddenly from thrombosis of a coronary artery				

Postmortem Summary. The kidneys show only slight lesions which consist of (1) traces of a former glomerulitis of the intracapillary type and (2) a moderate arteriosclerosis of the renal arteries with slight scarring of the cortex.

seen that their clinical peculiarities were paralleled and outlasted by a particular peculiarity in their urine.

It was observed that long after the edema and hypertension and gross hematuria had gone the rate of red blood cell excretion in the urine remained high and that this continued for months, even to a time when the rates of cast and protein and white blood and epithelial cell excretion were approaching normality. As an illustration we give counts made on a patient who developed the typical triad of symptoms while he was recovering from a cellulitis of the hand.

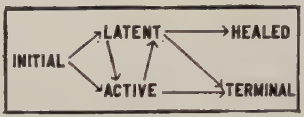

FIG. 10.

The death of this patient from coronary thrombosis five months after the onset gave us the unusual chance of relating the residual urinary abnormalities with the remaining anatomical defects, a matter of great importance for our present purposes. But in the development of the meaning of an increased rate of red blood cell excretion the many patients who were known to have suffered from edema, hypertension and hematuria after a streptococcal infection were of much greater significance. For it was by continuing the urinary measurements, not for months but for years, on a group of patients thus united by a common etiology and by an initial symptomatology of such unmistakably individual significance, that all the possible curiously diverging paths of development of the renal lesion came at last to be outlined. The arrows in the diagram (Fig. 10) indicate under the caption of an obviously provisional nomenclature the varying results which may follow from this one complex of conditions.

Here within one continuous series we have the greatest possible divergencies: patients who are distinguishable from the normal only by the most careful quantitative work along with those who are on the point of death; patients with entirely normal cardiovascular reactions, patients with transient hypertension, patients also with diastolic pressures which remain always far above the uppermost limits of normal variation; all degrees of edema, not only the soft and pitting form, but also the tense and brawny edema approaching the characteristics of the inflammatory type; patients with hemiplegias and monoplegias, transient or lasting; patients with convulsive attacks, or in coma; patients who have irrevocably lost their eyesight from extensive retinal lesions along with those who are blind only for a day. Also, and for our present purpose most important of all, we have here the greatest possible differences in the character of the urine. The rate of protein excretion varies from the normal average up to 25,000 mg. per twelve hours, from urines in which no protein can be detected by the heat and acetic acid test up to those which solidify on boiling. The casts vary from hundreds to many millions per twelve hours and comprise all forms of casts. In some cases blood casts and hyaline casts predominate; in others epithelial, granular, waxy and fatty casts are found in large numbers; in others only renal failure casts are seen. The epithelial cells and leucocytes vary in relative proportion from urines in which it seems clear that polymorphonuclear cells predominate to those in which only very large numbers of epithelial cells in all stages of granular and fatty degeneration are distinguishable. The volumes and specific gravities pass through all the gamut of possible variation, and the gross appearance of the urine includes instances of urines brown with hematin or red with hemoglobin, urines cloudy with degenerated epithelial cells or precipitated globulin, through all stages of dilution to the clear and watery urine of uremia. But all these diversities flow from one common source, and all are included within the unity of this one disease.

Bleeding is the obvious and striking abnormality in the initial stages of the renal lesion, and this sign continues when all other abnormalities have gone. Bleeding persists though the original characteristics of the lesion are overlaid and fall into relative insignificance under the intensity of a degenerative element. It continues even to the end when the secreting renal tissue has almost gone. Bleeding is the one never-failing manifestation, the one sure mark by which this disease may be recognized under all its manifold appearances. It is therefore in consonance with the empirical nature of this study that the disease should be called hemorrhagic Bright's disease.

In the early stages of an investigation when little is known and almost everything remains uncertain it is safer to use words which are not already heavy with meaning and which do not pretend to do more than summarize the essential facts of observation. If, for instance, this condition had been designated "inflammatory Bright's disease" the interestingly uncertain meaning of the word inflammation would at once have come to mind. If we had called it "glomerular nephritis" we should have been more specific than the clinical facts allow. The term hemorrhagic is an ugly and clumsy word but that is of little importance in comparison with the fact that it is truly descriptive and has a fortunate lack of any background of significance. Similarly in regard to the words "initial," "latent," "active" and "terminal" used to describe the different stages of the disease, it may be said that at least they are non-committal and free from complicating connotations.

Initial Stage: The first count given in Table xii is typical. The patient was a man of middle age who, following an injury to his finger, developed a cellulitis of the hand with a lymphangitis of the arm. Eighteen days later, when the infection had already subsided, he developed an edema of the face. He was seen at once and found to have a generalized brawny hard edema most evident in the face and legs. His blood pressure was 185 systolic and 115 diastolic. The urine looked like rather dilute cloudy coffee. Here, then, was one of this specific group of patients, for we have the appearance of edema, hypertension and hematuria during convalescence from what may well have been a streptococcal infection. On the next day a twelve hour's collection of night urine was obtained after abstention from fluids. The volume was 238 c.c. per twelve hours, a value less than the normal average of 381 c.c. but still well within the range of normal. The specific gravity was 1.020 which is much below the limit of normal variation and would have been still lower if a correction had been made for the 2400 mg. of protein in solution in the urine. The blood urea concentration was 98 mg. per 100 c.c., a significant figure since the patient was feeling quite well. The extent of the lesion could not be measured because we failed to produce diuresis by administering water. The gross appearance of the urine was in itself pathognomonic, for this particular combination of blood, leucocytes, epithelial cells and casts combined with an acidity which converts the hemoglobin into brown acid hematin is not duplicated in any other condition. The differential count of the 1,190,000 casts is given below:

	Per Cent
Blood casts	25
Epithelial casts	11
Granular casts	17
Fatty casts	6
Waxy casts	4
Hyaline casts	37
Renal failure casts	0

It will be noted that in these blood casts we have evidence that the blood comes from the kidney and furthermore penetrates into the tubules and though it is not yet demonstrated that it comes from the glomerular tufts that is at least its probable site of origin. For this reason blood casts have a quite special significance and in such cases as this there is opportunity to learn all their varied forms and appearances. It is unfortunate that the textbooks of clinical pathology figure as blood casts only those pure forms in which the red blood cells remain distinct and unaltered. These constitute only a small minority of all blood casts. In this initial stage most of them are really partly blood and partly epithelial casts and consist of all grades of mixtures of red blood cells and epithelial cells. They can be differentiated into blood casts and epithelial casts only by a judgment as to the preponderance of one or the other type of cell. All of them are stained in various shades from light yellow to deep brown in accordance with the amount of hematin they contain.

The blood and the blood casts are the essential and never absent characteristic of the initial stage but the count reveals much more than bleeding. In this twelve hours' urine there were 57,000,000 white blood and epithelial cells, while the average in normal individuals is only a little over 300,000. Furthermore the appearance of many of these cells suggested that a quite active degenerative process was at work in the kidney for they were swollen and filled with coarse granules. The differential cast count also revealed that a considerable proportion of all the many casts were of the epithelial type and the cells within these casts were granular. So though we may call this lesion hemorrhagic we have evidence that the term is incomplete and that it would be more adequately described as a hemorrhagic-degenerative lesion. There is finally another characteristic peculiar to this initial stage for which we can however give no numerical evidence. It is here that one is frequently impressed by the number of polymorphonuclear leucocytes, though the poor preservation of most of the cells makes any enumeration difficult and uncertain. But it remains true that more leucocytes occur in the initial stage than are to be found at a later time.

LATENT STAGE: We can again refer to Table XII for an illustration of a transition from the initial to a latent stage. The exact point at which this occurs cannot be exactly defined, for there is a smooth and gradual change from a state of active capillary bleeding and intense degeneration to one in which there is very little blood and no certain evidence of any degenerative process. This ill-defined point is passed long after the subsidence of the edema and hypertension. In this particular patient the edema had disappeared in a few days, the hypertension probably lasted longer, but when he was seen again twenty-seven days after the onset the blood pressure was 130 systolic and 70 diastolic. The turning point came about the fifty-fifth day when the rate of protein excretion had fallen to 324 mg. per twelve hours, the casts over the same period numbered 208,000 and the white blood cells and epithelial cells 5,400,000. At this time there were still 176,000,000 red blood cells per twelve hours, enough to make the urine slightly smoky. Twenty per cent of the casts were blood casts, 10 per cent were epithelial and the remainder were hyaline. By the ninety-sixth day he was quite definitely in the latent stage, the urine had an entirely normal appearance, the rate of protein excretion was only 65 mg. per twelve hours, there were now only 33,300 casts and 4,700,000 white blood cells and epithelial cells. There were still however 85,000,000 red blood cells per twelve hours. The table shows still further stages of subsidence in the intensity of the renal lesion. It is at this time particularly that the finding of blood casts lends certainty in the diagnosis of cases that are first seen long after the initial stage has passed unnoticed or been forgotten. These casts now contain no epithelial cells and in most cases there are also no recognizable red blood cells so that they are to be distinguished only by their color. They are orange or brown casts full of granules. In some cases the red cells have agglutinated into rounded masses and clumps. Occasionally the indistinct outlines of red blood cells can still be seen. Counts from the four patients who supposedly died in the latent stage are given in Table XIII.

Table XIII

Hemorrhagic—Latent

Name	No. of casts in 12 hrs.	Differential count (per cent)					R.B.C. 12 hrs.	W. & Ep. 12 hrs.	Prot. mg. 12 hrs.	Vol. / Sp.Gr.	Blood urea
		Bl.	Ep.	Gr.	W.	Hy.					
Thomas Z..........	19,100	15	..	15	..	70	68,000,000	1,210,000	29	$\frac{202}{1,000}$	36
Patrick F..........	112,500	82	8	6	..	45	Many	....	50	$\frac{105}{1,019}$	43
Floyd, Mc C........	211,000	5	10	25	..	55	27,600,000	7,140,000	320		
Mark T............	....	6	..	..	2	92	Very many				
John M...........	21,000	46	0	41	0	13	Many	....	276	.....	58

Active Stage: This stage may be continuous with the initial stage, or it may develop after an interval of latency. In 11 of the patients described here who died in the active stage and whose course is sufficiently known there were 7 in which there was no interval between the initial and active stages, while in 4 there was an intervening time during which the lesion became latent. The word active is used here rather with reference to the general clinical picture than as a description of the renal lesion, for which it is a too general designation. It is the stage of activity in symptomatology in contrast to the inactivity of the latent stage. This is true especially of edema. It is now a soft pitting edema different from the hard edema of the initial stage. There is also always accompanying this symptom a rate of protein excretion of several grams per twelve hours. The association may well be significant for there is accumulating evidence that this particular type of edema is conditioned by a lowering of the concentration of plasma albumin. With respect to the urine sediment it is the evidence of an active degenerative process which is particularly predominant and it is this element which often outweighs all others in the microscopical examination. The shining fat droplets on all the casts, the many "oval fat bodies," which are greatly swollen renal cells full of fat droplets and granules, the doubly refractile fat globules within the cells and casts and lying free in the urine, all these make a very striking picture. By contrast the hemorrhagic element seems faint and uncertain. There is usually no longer any obvious hematuria. The urine is now more dilute and in consequence the red blood cells are only pale ghosts, mere stromata from which the hemoglobin has gone. Without care and experience they will not be seen and then only the lipuria, the

TABLE XIV

HEMORRHAGIC—ACTIVE

Name	No. casts in 12 hrs.	Differential count							R.B.C. 12 hrs.	W & Ep. 12 hrs.	Prot. mg. 12 hrs.	Vol. / Sp. Gr.	Blood urea	Amount of renal tissue
		BL	EP	GR	FA	W	HY	Renal Failure						
Kelly B......	107,000	..	..	..	..	..	..	100	452,000,000	30,000,000	2,641	143	189	
Robert B.....	1,030,000	..	4	2	..	8	86	...	1,890,000,000	79,500,000	4,354	295 1.013	80	
Peter B......	....	..	..	..	..	..	..	100	Gross hematuria	....	.....	625 1.014	363	
Helen F......	....	+	+	+	..	..	+	...	Gross hematuria					
Helen G......	1,390,000	..	+	+	..	..	+	+	10,600,000	5,900,000	1,140	320	125 27	
Henry G.....	296,000	..	4	..	4	..	92	...	1,860,000	91,600,000	1,750	.....		
Alparata H...	296,000	..	+	+	..	..	..	+	192,000,000	15,000,000	857	555 1.009		
Edward R....	221,000	..	2	..	..	2	96	...	172,000,000	31,000,000	2,390		69	
Eugene Mc V.	13,600	5	..	5	..	15	75	...	615,000,000	50,500,000	2,010	931 1.014		
George O.....	2,970,000	..	..	8	8	..	84	...	53,000,000	56,000,000	2,910	267 1.020	75	
James R......	Large numbers	..	+	+	+	+	..	+	Large numbers	Large numbers	.....	.....	206	
Adolph S.....	2,300,000	12	15	18	..	3	25	27	24,000,000	62,000,000	220	760 1.014	...	38%
Robert T.....	4,075,000	..	2	..	2	1	82	13	5,920,000	36,250,000	2,870	290 1.023		
Marion B....	+	..	..	..	..	..	..	100	+	+	+	.....	456	
Jane S.......	23,000	..	..	50	..	10	16	24	2,050,000	3,700,000	2,768	64 1.023	160	

heavy proteinuria, the massive edema, the lipemia, the hypercholesterolemia, the lowered basal metabolism and the frequent absence of increase in blood pressure and in the non-protein nitrogen concentration of the blood are left and all these tend towards another clinical diagnosis of "nephrosis." But these pale and unnoticed cells remain as witnesses to the continued existence of a hemorrhagic renal lesion which will in the end determine the patient's fate.

Most of the counts given in Table XIV which are abstracted from the records of those patients who died in the active stage show very high rates of excretion of red blood cells. These were stormy cases in which there was a true general activity of the renal lesion in all its aspects. When the lesion is less intense the patient generally lives until the reduction of renal tissue ushers in the terminal stage and during the active stage in such cases the red cell counts are only in the millions or tens of millions so that the hemorrhagic element is relatively inconspicuous in contrast with the pronounced evidences of renal degeneration.

TERMINAL STAGE: This is the stage of a conspicuous failure of renal function. The characteristics of the urinary sediment are determined by the failure of the kidney. For a consequence of this failure is a marked increase in the concentration of urea in the blood, and such an increase is accompanied even in normal individuals by a dilution of the urine, as if the mere presence of an excess of urea in the blood were associated with an increase in the quantity of water available for excretion.[29] If we accept the current conceptions of the functional topography of the kidney we may also consider the influence of the reduction in the number of renal elements and the effect of tubular lesions on the reabsorption of water. But whatever the relative importance of these factors the fact remains that in this stage the urine is invariably dilute and remains dilute even though for a time no water is consumed. And so when this stage is fully developed the sediment is radically altered by a purely physical mechanism, for the hyaline casts which up to this point have been so numerous must necessarily dissolve in such dilute urines. But there is more than this, something less simple and harder to interpret. We can understand why the number of cells and the number of casts of the epithelial type tend often to diminish in number as the lesion progresses. That is because there are fewer renal elements still functioning. But why is it that as the blood urea concentration rises higher and higher the casts tend to become broader and broader? Since the breadth of a cast is determined by the diameter of the lumen of the tubule within which it forms it seems at first reasonable to associate this phenomenon with the dilation of the tubules which is so prominently shown in sections of contracted kidneys. These dilated tubules are often seen to be filled with casts and it might seem that here we had direct clinical evidence of a particular anatomical defect. But the facts are conclusively against any such interpretation. In the first place the breadth of these casts in no way corresponds to the extremely irregular cystic dilations in the cortex of fibrosed kidneys, and, secondly, they are found in the urine from kidneys in which no dilation of the tubules exists. The only abnormality constantly associated with the occurrence of renal failure casts is a high blood urea concentration due not to any unusual formation or ingestion of urea but arising directly from a failure of renal function. The failure is not the result of any particular anatomical type of renal lesion for renal failure casts have been found in recovery from calculus anuria, in degenerations due to mercury, and in urine from amyloid kidneys and from polycystic kidneys as well as in the terminal stage of hemorrhagic Bright's disease. They are evidently manifestations of a particular functional state of the kidney. The urine is always dilute but the rate of urine excretion must not be too high, for if water is given in large amounts and the urine volume thereby somewhat increased these casts disappear. It is largely perhaps because uremic patients are

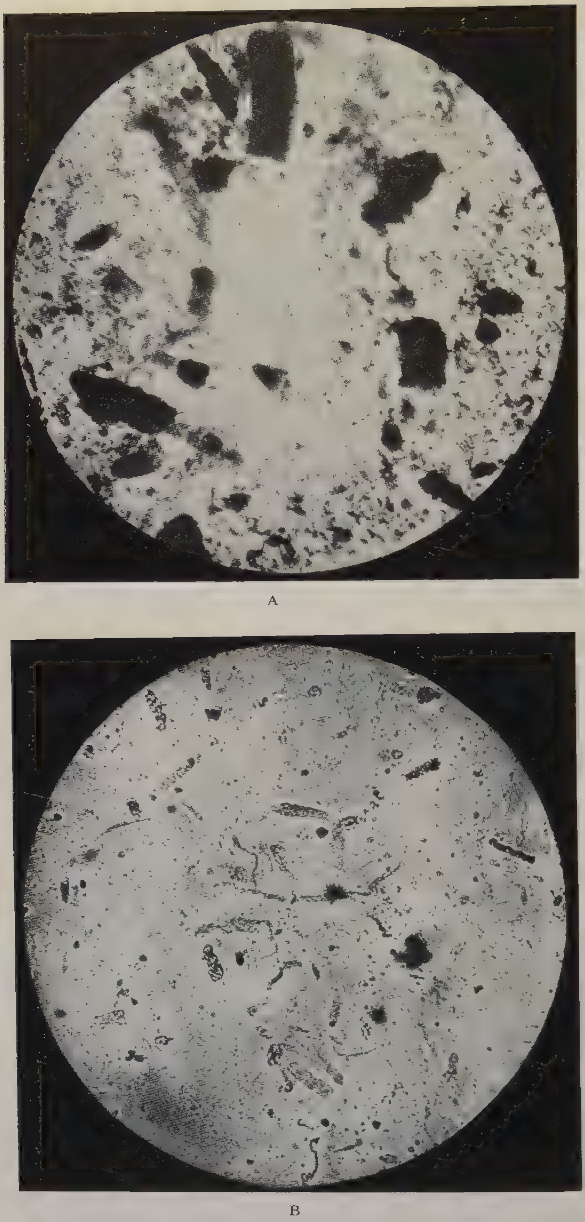

FIG. 11. A. Renal failure casts. (× 82) B. Hyaline and fatty casts of ordinary breadth. (× 82)

flooded with water or given intravenous injections of salt or sugar solution that this very interesting and striking peculiarity of renal failure has for so long been overworked. In all cases where renal failure casts are found we have a high blood urea concentration due to a renal lesion of varying type but producing always a urine containing, in the earlier stages, casts of the usual form and breadth. As the blood urea concentration rises and the urine becomes less concentrated the ordinary casts disappear and are replaced by renal failure casts, whose appearance is distinctive even apart from their unusual breadth. There can be no question that they are formed by the agglutination of epithelial cells. In some the cell outlines can still be clearly distinguished. Even the oval nuclei can sometimes be seen and occasionally cells with two nuclei. But more often they have a glassy refractile appearance with only faint remnants of any cell outlines and between these structures and typical broad waxy casts there are all possible gradations. But the epithelial casts most frequently follow another pathway of degeneration. They disintegrate into granules and come to form the broad coarsely granular casts which are shown in Figure 11.

The breadth of these casts corresponds to the breadth of the lower reaches of the collecting tubule system. They are to be seen as will be described later by the Pathologist in the papillae of the kidney in the tubules of Bellini.

It is perhaps not wise to speculate but it seems plausible to suppose that in uremia, which is due to the cessation of function in most of the renal elements, there may be such a rapid flow of urine down those elements which still remain active that the desquamated cells which usually clump into casts at a higher level are now washed down into the broad collecting tubules and only there are able, under favorable conditions, to agglutinate together into the loose and friable structures which we have called renal failure casts.[4]

TABLE XV

HEMORRHAGIC BRIGHT'S DISEASE—TERMINAL STAGE

Name	No. casts in 12 hrs.	Differential count (per cent)							R.B.C. 12 hrs.	W & Ep. 12 hrs.	Prot. mgm. 12 hrs.	Vol. sp. gr.	Blood urea	Ratio per cent of normal
		BL	EP	GR	FA	W	HY	Renal Failure						
Percy B........	111,000	..	..	..	..	..	..	14	5,000,000	2,500,000	2,605	495 1.011	74	
Frederick B.....	170,000	..	..	..	..	..	..	100	10,600,000	1,900,000	3,213	425 1.014	126	
Richard B......	239,000	..	..	..	..	..	..	100	109,000,000	51,000,000	3,100			
John A. B......	....	..	..	..	..	..	..	100	....	....	2,530	.....	105	
John B........	642,000	..	..	..	..	4	12	84	970,000,000	89,000,000	5,870	660 1.015	359	
Nicholas C.....	580,000	..	..	..	..	..	..	100	5,900,000	2,400,000	920	154 1.013	317	
John C.........	0	..	..	..	..	..	..	...	2,650,000	(506,000,000)	2,363	550 1.018	636	
Lucy C.........	28,500	..	..	..	..	..	..	100	85,000,000	162,000,000	.....	127 1.015	216	
Richard C......	114,000	..	..	..	..	..	..	100	Many	....	1,020	1.010	331	3
Stewart D......	....	..	..	..	..	..	..	100	Many	Many	.....	375 1.008	391	
Edith D........	360,000	..	..	..	..	..	..	...	18,900,000	....	5,760	750 1.013	227	
Ernest G.......	27,000	..	..	..	..	..	..	100	113,000,000	5,000,000	.....	873 1.009		
Margaret G.....	11,000	..	..	..	..	..	..	...	4,500,000	5,600,000	1,500	248 1.016	445	
Elizabeth G....	0	..	..	..	..	..	..	...	....	Pyuria	1,330			
Charles H......	340,000	..	..	..	..	..	..	100	2,400,000	3,640,000	1,560	776 1.013	196	
Geneva K......	125,000	..	..	..	..	..	..	100	2,700,000	109,000,000	3,094	773 1.013	289	
Bertha K.......	Many	..	..	..	..	..	..	...	Many	Many				
Leo N..........	38,000	..	..	..	..	..	..	100	4,800,000	9,000,000	2,160	475 1.014	332	
Ralph S........	116,000	..	..	..	..	..	..	100	49,800,000	4,500,000	2,810	708 1.014	206	
William V......	239,000	..	..	..	..	..	..	100	12,000,000	11,000,000	1,520	.....	465	
Leila B........	0	..	..	..	..	..	..	..	6,200,000	18,000,000	5,020	1.035 1.013	450	
Nathaniel C....	0	..	..	..	..	..	..	..	12,700,000	210,000	460	636 1.011		
William C.....	44,500	..	..	..	..	..	..	100	12,800,000	1,500,000	589	520 1.011	262	
Verna G.......	0	..	..	..	..	..	..	..	1,000,000	8,000,000	2,756	319 1.014	383	
John W........	Many	..	..	+	..	+	..	+	Many	......	2,880	low	350	
William Z......	0	..	..	..	..	..	..	..	9,000,000	800,000	1,357	880 1.010	140	

In Table xv are counts from the patients of this series who died in the terminal stage. It is worth noting that in all cases the rate of protein excretion was high. This has been confirmed in many other cases in which no postmortem examination was made and the constancy of this manifestation makes it possible to exclude by this very simple observation the possible existence of a terminal glomerular nephritis in the pseudouremia of arteriosclerosis. Along with this proteinuria there is always some and usually quite pronounced evidence of a desquamation of renal cells. It is in this stage particularly that one finds millions of epithelial cells which quite clearly are not leucocytes. Since they seem to increase with the mounting blood urea concentration it seems as though there were a connection between the abnormality of the blood and the death of the renal cells, as if the kidney through its failure were contributing directly to its own final complete disintegration.

In spite of the diluteness of the urine the red blood cell excretion is always abnormally high. The counts are probably often too low because many of the cells are entirely lyzed but enough are left to carry on to the end the sign of blood in which the lesion was initiated.

Degenerative Bright's Disease

For the purpose of this study we include under the name "degenerative Bright's disease" all the very numerous conditions which are associated with the appearance of evidences of degeneration of the renal parenchyma without bleeding. But here, in contrast with hemorrhagic Bright's disease, we have no unity but only a collection of diseases of very diverse etiology connected by the circumstance that they all in some degree lead to proteinuria, cylinduria and in particular to an increase in the rate of excretion of degenerated epithelial cells. Under this category comes the renal degeneration associated with the late toxemia of pregnancy, the cloudy swelling which accompanies so many generalized infections, the degeneration or necrosis of the tubule cells produced by mercury, uranium and chromium salts and the lesions produced in jaundice or in severe malaria. There are also the degenerative changes which so often follow or precede the deposition of amyloid in the kidney. Finally there are some patients in whom evidences of degeneration are found apart from any apparent cause.

There may be within the group thus loosely connected by a general similarity in the nature of the urine sediment great differences in the location and extent of the renal lesion. There is no clinical reason why we should suppose that we are dealing here only with lesions of the tubules any more than in hemorrhagic Bright's disease it is possible to believe that the lesions are only glomerular. But we do know that in the latter case the lesions are of such a nature as to lead to an excessive bleeding not found here. Unfortunately we know almost nothing with certainty about many of the lesions in this group because in uncomplicated cases the opportunities for anatomical study so seldom come. Here we can collect only cases which may be grouped under three subdivisions, 4 cases which we have to range under the group of unknown etiology, 2 cases in which non-bacterial poisons were responsible, 5 cases with long-continued suppuration complicated by amyloid deposition, and one which was thought to be due to staphylococcal infection.

The counts given in Table XVI show in general a high rate of excretion of epithelial and white blood cells and an intense proteinuria, with few or no red blood cells. The one exception in this latter respect was a patient who was seen shortly before his death from an intense malarial infection.

It is the patients with degenerative Bright's disease in whom the condition arises not simply as part of another disease but independently of any cause which can be discovered who are of particular interest both to the clinician and the pathologist. These cases have been called cryptic degenerative Bright's disease in order to emphasize our lack of knowledge as to their

TABLE XVI

DEGENERATIVE BRIGHT'S DISEASE

Name	No. casts in 12 hrs.	Differential count (per cent)							R.B.C. 12 hrs.	W & Ep. 12 hrs.	Protein mgm. 12 hrs.	Vol. sp.gr.	Blood urea	Ratio per cent of normal
		BL	EP	GR	FA	W	HY	Renal failure						
							Cryptic							
Otis E.	807,000	..	..	..	5	..	F* 95	..	0	27,200,000	1,840	210 1.032	71	
Mildred F.	Many	..	..	..	+	..	F +	..	Few	Very many	12,600	.....	15	95
Frank V.	82,000	..	..	..	..	..	F 100	..	0	17,200,000	4,470	265 1.032	41	
David R.	276,000	..	..	3	..	3	F 94	..	Few	Very many	....	.....	63	
George D.	Many	..	..	..	..	..	+	0	....	....	....	.....	......	.....
							Pyogenic							
John R.	330,000	..	1	..	11	12	F 76	..	0	Very many	11,000	1.030	38	
Benjamin C.	1,180,000	..	..	..	..	..	..	..	0	4,400,000	....	220 1.019	12	
Henry C.	....	..	..	..	..	..	+	..	Few	Pyuria	Large amount	700 1.014	87	
Leonard C.	237,000	..	13	2	..	..	F 85	..	Few	Many	8,500	564 1.023	61	
William H.	....	..	..	..	..	6	94	..	....	....	16,500	1.125 1.014	78	
							Non-bacterial							
Adam B.	....	..	..	..	..	..	+	..	Few	Many	Large amount			
Alonzo P.	310,000	..	4	..	..	..	..	96	15,000,000	5,700,000	Moderate amount	.....	422	
							Bacterial							
Paige C.	1,815,000	..	5	57	..	5	23	..	0	25,700,000	3.171	143 1.024	72	

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* The letter F indicates that these casts were sprinkled over with shining fat droplets.

origin and also to show that they are regarded as examples of a true disease entity. But the grounds for this opinion, for it is only an opinion, lie beyond the scope of our present interests and we refer to the clinical and anatomical records of our 4 patients as partial but quite inadequate evidence in its support.

The group we have called progenic were patients with long-continued suppuration who on clinical grounds were thought to have waxy disease. But we have avoided the use of the word amyloid kidney, because the urine does not give direct evidence of the presence of this abnormality. It is always an extracellular deposit and never reaches the urine. All we know directly is the evidence of tubular degeneration which so often, perhaps always, is found in the urine from kidneys in which a large quantity of amyloid material has been laid down. But certainly in the early stages of waxy disease there may be no appreciable renal degeneration and it seems more accurate to regard the amyloid and cellular degeneration as two associated but partially independent effects.

Of the non-bacterial group we have only 2 cases, one patient with carcinoma of the gallbladder and an intermittent gallstone obstruction of the common duct, who died, deeply jaundiced, after a course of neoarsaphenamine. The other patient was a sailor who had just arrived from Mexico. He had an extremely intense malarial infection and was comatose. The urine contained large numbers of renal failure casts and they and all the many cells in the sediment were deeply stained with blood pigments. There were also 15,000,000 red blood cells in twelve hours urine but in view of the general clinical situation this hematuria was, of course, not regarded as carrying its usual significance and the case was classified as one of degenerative Bright's disease.

We have thus shown that what we call degenerative Bright's disease comprises a heterogeneous collection of patients suffering from many unrelated diseases. It is evident that we are classifying not diseases, but renal lesions, for certainly it can only be as attention is directed solely towards the kidney that any connecting link between such clinical diversities is to be discovered. But even in this respect the association has the appearance of representing only that sort of illusionary relationship which is the fruit of ignorance. Is there in fact any reason why this degenerative Bright's disease should be regarded as more than a sort of temporary dumping ground onto which can be thrown all the renal lesions with neither the characters distinctive of hemorrhagic Bright's disease, nor the peculiarities which allow them to be grouped under arteriosclerotic Bright's disease? Are there not, in actual fact, excellent reasons, even from the purely clinical standpoint, for the belief that the renal lesions we thus range under this one heading are in actual fact no unity at all? May there not be groups within it which differ from one another by more than degree or intensity? In the end may not these groups, in accordance with their diverse etiology, be shown to possess each one its own separate individuality? Has not Susuki[30] demonstrated how anatomically distinct are the renal lesions produced by inorganic salts such as those of mercury, uranium and chromium? May not, therefore, the different organic poisons formed in various diseases leave each their own particular and characteristic mark on the kidney?

But over and beyond the increase in the rate of excretion of degenerated epithelial cells without an accompanying increase in red blood cell excretion, which originally gave occasion for this separation, there does exist a reason for the association of many renal lesions under one heading. And it is not merely an academic and formal distinction but one which is of the utmost importance to the clinician in his daily practical work. This clinical justification consists of the fact that all the renal lesions in the degenerative group are reversible in nature and so are to be separated from the irreversible lesions of hemorrhagic Bright's disease and renal arteriosclerosis. For consider the main clinical groups which are associated with renal lesions of the degenerative type. What could be more dramatic than the complete and sudden reversion to normality in the late toxemia of pregnancy? Here are all the clinical evidences of a most intense degeneration. A urine small in amount, containing protein in a concentration so high that the urine solidifies when it is boiled, full of epithelial, granular, and hyaline casts, and of cells which contain coarse granules and fat droplets. And yet within twenty-four hours of delivery everything has quieted down and in a few weeks there may be no trace of the existence of a renal lesion of any sort. Less dramatic but no less certain is the disappearance of the "febrile albuminuria" which follows recovery from infection. From experimental as well as from clinical observation we know how quite completely all traces of clinical and structural renal abnormality vanish in patients who recover from corrosive sublimate poisoning. But when we come to amyloid disease we meet a renal lesion which general clinical experience seems to show proceeds remorselessly and irreversibly towards a complete destruction of the kidney tissue. There are not wanting, it is true, indications that this is no necessary fate. In 1866 Bartels[31] recounted the case of a patient with typical amyloidosis who completely recovered. But the proof of the reversibility of this lesion was not given until 1928. In cases of long-continued suppuration of the extremities Waldenström[32] proved the existence of amyloid disease by excising a portion of the liver. He then amputated the diseased limb. He demonstrated the subsequent disappearance of all clinical evidences of waxy disease, including the disappearance of proteinuria and cylinduria, and finally he proved by means of another biopsy that the amyloid matter had been entirely absorbed. Finally we come to the patients in whom there seems to be no reason for an often intense degenerative renal lesion. This is the small and much disputed group of patients with "genuine nephrosis." And here too we have a reversible renal lesion for I, and many others, have seen most typical cases of this obscure disease progress to a complete recovery.

It is only natural to think of the observed clinical reversibility of the lesions of degenerative Bright's disease as an expression of the capacity for regeneration of the renal cells. We know that in those types of renal injury which are produced by mercury there may be a perfect regeneration even though many of the cells have been destroyed. So long as in each section of a renal element some cells remain viable all may in time live again. And it is also natural, though only as an hypothesis, to think of clinical irreversibility as an expression of that sort of lesion in which the architecture of the kidney has been so altered as to interfere with the exchange of material between the renal cells and the lymph and blood plasma.

But altogether apart from the mechanism of reversibility it is clinically useful to group under one heading all the renal lesions in which a restitution to the normal is possible. It enables the physician to deal with equanimity with some of the unnecessary fears which beset his patients, for, in so far as the renal lesion is concerned, there is nothing here which is beyond hope. And there is another clinical aspect which is of yet greater value. To place a patient in this division is equivalent to looking through the kidney towards the conditions which have produced the lesion. For in all cases of degenerative Bright's disease the renal lesion is of secondary, not of primary, importance. From the clinician's point of view it deserves an exact and careful study only in so far as that may aid in the discovery of the conditions, and especially of the removable conditions, which lie behind it.

Arteriosclerotic Bright's Disease

Every clinician and every pathologist will understand that by "arteriosclerotic Bright's disease" is meant the renal lesion which is associated with arteriosclerosis of the renal arteries and arterioles, and it is for this reason that we have used the term in spite of the fact that in doing so we leave the safe ground of pure empiricism and simple description and introduce an anatomical assumption into a classification which purports to rest only on actually observed clinical facts. The inconsistency, of course, is purely verbal and of no moment in a classification which does not pretend to be more than a temporary convenience. It is an unimportant and formal inconsistency because in actual fact cases are relegated to this group not on account of any clinical speculation as to the state of the renal vessels but because the counts made on the urinary sediment reveal neither the characteristics which we have described for hemorrhagic nor for degenerative Bright's disease, but show instead a steady low rate of protein and cast excretion with no marked abnormality in the rate of elimination of any sort of cell, combined with a slowly developing but often in the end a considerable reduction in the quantity of secreting renal tissue.

In spite of the fact that this diagnosis is reached largely by exclusion it carries a sense of assurance which is almost a necessity for the management of by far the largest proportion of all those patients who are generally regarded as suffering from Bright's disease. It is an assurance to be obtained only by a direct quantitative study of the urinary sediment by the clinician himself. For consider the everyday situation which is forever recurring. A middle-aged man applies for life insurance. A routine urine examination reveals albumin and casts and his blood pressure is found to be high. He is told to consult his physician. But of course he first consults his own knowledge and experience. He has had friends who are said to have died of Bright's disease. He has a vague idea of terrible consequences, of blindness, paralysis, convulsions. A fear begins to waken within him which he strives to suppress. His blood pressure rises to still higher levels. He wakes in the morning with a dull headache, he begins to observe a buzzing in his ears and at times he is dizzy. If in such a state he sees or senses that his physician is not quite sure about the nature and outcome of his renal disease, no reassurance will comfort him, no reordering of his habits will cure him. Of course he can be cured of this fear. But there is only one cure, a complete and absolute assurance. The immediate source of the assurance is immaterial. For a time at least he may be suddenly cured by the assumed assurance of the quack with some special medicine or diet. More slowly but forever he is usually cured by attaining to some faith which makes him indifferent to the consequences he once dreaded. But his physician as a rule has neither the self-assurance of the charlatan nor always the attitude of mind which might suggest the possibility of that lasting internal assurance which alone can really save. The patient's attention is fixed on the results of routine urine examinations, of phenolsulphonephthalein tests and of blood pressure measurements. And the more honest the physician the worse will be the result. For the truth is that none of the accepted methods of clinical examination are able to differentiate with any certainty between the small number of patients who are going to die within a year or two of renal failure and the great majority who may live for decades and die of some intercurrent disease or from cardiac decompensation or cerebral thrombosis or hemorrhage. And so in the end there is conveyed to the patient's mind a sense of uncertainty which augments his fear. Consider on the other hand the assurance of the clinician who not only hopes but knows as a result of his own objective measurements that this particular patient has an inactive renal lesion, without the marked increase in the rate of red blood cell excretion which he invariably finds in the urine of pre-uremic patients. That assurance passes quite inevitably from the physician to the patient and gives him time to adjust himself to the realities of his situation.

But the clinical realities of arteriosclerosis are for us beside the point. Here we have only to consider the consequences with respect to the kidney and in particular to enquire whether quantitative urinary sediment examinations enable us to predict the nature of the renal lesion. The case of John H. may be cited as typical and uncomplicated. He had been under observation for many years on account of hypertension. Counts made between 1924 and 1927 are given in Table XVII.

TABLE XVII

Date	Protein, mg. per 12 hours	Cast excretion, No. per 12 hours	Red blood cells, No. per 12 hours	White and epithelium cells, No. per 12 hours
March 12, 1924	20	8,200	945,000	580,000
March 31, 1925	20	17,100	830,000	308,000
May 18, 1926	..	4,500	0	162,000
April 4, 1927	82	3,200	105,000	23,000

The protein excretion is only once abnormal, and casts are only in the thousands or tens of thousands, the white blood and epithelial cells are always within normal limits, and most important the number of red blood cells, though on two occasions they passed the bounds of normal variation, never exceeded 1,000,000 per twelve hours. Therefore this cannot be the latent stage of a progressive hemorrhagic lesion. If there had been only one examination one might have regarded it as a minor lesion of the general type we have called degenerative Bright's disease supposedly produced by some undefined infection or toxemia. But this is not simply a transient irritation for it remains the same over a period of years. Though inactive it is lasting.

In Figure 12 the extent of the renal lesion is charted. This lesion which seemed so slight as judged by observations on the urinary sediment is nevertheless associated with a very slowly progressive but considerable decrease in the amount of functioning renal tissue, for in the end only about half of the normal quantity to be expected in a man of his size remained.

There is here then the parodoxical conjunction of a lesion which judged from one aspect is of almost vanishing significance and yet from another has sufficed to destroy half of the original amount of kidney tissue. It is a situation which demonstrates most clearly the fallacy of trusting implicitly to quantitative urine examinations for the purpose of reaching towards a clinical judgment even in regard to such a relatively small matter as the renal condition of a patient. But it also enables us to give a new interpretation to these apparently insignificant urinary abnormalities. For what sort of lesion other than a slow fibrosis could lead to the cessation of function of so large a proportion of the total kidney substance without at any time giving evidence in the urine that an actively destructive process was at work? What lesion might be expected to lead to a slight increase in the number of casts and cells over periods of years other than a malnutrition of certain areas of the kidney as the blood supply fails on account of a slow vascular occlusion? Though indirect and negative the evidence is not inconclusive.

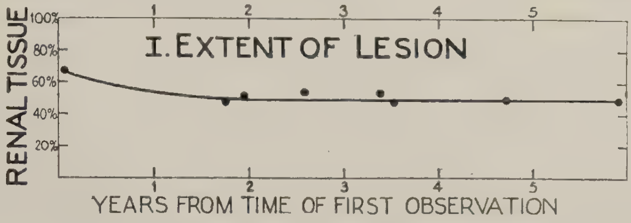

FIG. 12. Arteriosclerotic Bright's disease.

There is, however, a question which remains before such an interpretation can be provisionally accepted. The graph (Fig. 12) shows that over a period of five years the amount of renal tissue remained constant. Now renal arteriosclerosis is an irreversible process and if we take the urinary sediment results as evidences of a malnutrition of certain areas of the kidney preparatory to their atrophy and fibrosis, we are obliged to conceive of this vascular lesion as progressive and as leading to the death of more and more of the actively secreting renal tissue. How can an irreversibly progressive lesion, even granting that it is slow, leave the amount of functioning renal tissue the same over a period of five years? The same question arises in the latent stage of a hemorrhagic lesion, which we also conceive of as progressive and irreversible, but which nevertheless has been observed to leave the quantity of renal tissue practically unaltered over as long a period as ten years. An explanation is possible if we consider that here we are witnessing a particular example of a tendency established as true for the mammalian kidney in general, by virtue of which the death or removal of some of its renal elements is followed by an increase in the size of those which remain. Since it has been observed that this restitution of structure and function through hypertrophy does not occur when there is an interference with the blood supply of the remainder[33] we are led to suppose that in renal arteriosclerosis the lesion is probably not diffuse but focal. It is because the disease is limited to certain areas of the kidney and because the continuous destruction of renal tissue is met by a continuous restitution through compensatory hypertrophy that it is possible to meet with assurance the fears of patients with respect to uremia.

The foregoing case has been cited as typical and this may be true if we define as typical the mean of all cases of arteriosclerosis. But as with hemorrhagic Bright's disease so here also the term includes a great variety of clinical conditions. Repeatedly it has been noted, and instances are given later in detail, that at the end, when the patient comes to die from cardiac failure, the hitherto inactive renal lesion may be transformed and wear all the characters of an active degenerative lesion, with a high rate of protein excretion, many casts and large numbers of degenerated epithelial cells. But apart from such circulatory complications, there is the great variability which comes from the difference in the tempo of the arterial disease. In some degree renal arteriosclerosis seems to be the heritage of all individuals who pass the age of forty-five, though in the vast majority the rate of progression is so slow that death comes under some other form. Then come the great bulk of cases of patients in whom hypertension has been discovered who usually live so comfortably and so long even though in the end their hearts may fail or their cerebral arteries rupture. Beyond them lie a small group through which one can follow a steadily augmenting rate until the curve of intensity turns steeply upward and we are within the area which, though uncertainly and for somewhat arbitrary reasons, has of late been mapped out as an almost separate disease under the name "malignant sclerosis." We have some fragmentary evidence that the intensity of the disease in the kidney is sometimes paralleled by changes in the protein, cast and cell counts in the urine and so it comes about that in the most rapidly progressive cases one comes at last to sediments which are indistinguishable from those seen in the terminal stage of hemorrhagic Bright's disease. No separation is possible then except on the basis of previous urinary observations. These reveal the very different roads which thus converge towards the same end. Renal arteriosclerosis does thus occasionally culminate in uremia but that type of uremia is only a partial expression of a more general arteriolar dissolution.

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Chapter V

THE PATHOLOGICAL METHODS

Chapter V

THE PATHOLOGICAL METHODS*

Purpose of the Pathological Methods

Our co-author as an introduction to his consideration of the clinical aspects of the renal lesion in Bright's disease has devoted a section to the "purpose" of his investigations. No better approach, we feel, can be made by the Pathologist to his specific problem, for as will be apparent in what follows, if the latter's "purpose" does not need explanation, at least his "manner" may well require justification. For the reader will search in vain for the two salient features which distinguish the worth-while "Contribution to Pathology," namely, a critical and comprehensive consideration of the literature and the discovery of new and interesting facts. What is disclosed is in great part that which has been long known, so long in fact that it is a matter of common knowledge even to the clinician whose interest perhaps has not in the recent past been concentrated on the intricacies of abnormal renal morphology.

All this is not offered in apology or as in any sense an excuse for the purpose and manner of our presentation. We feel that though it lacks the conventional attributes which we have described, nevertheless since these methods and values have been maintained in the interminable series of descriptive investigations which have followed Richard Bright's first statement of the rudiments of the pathological lesions of the disease which bears his name, and since no strikingly successful conclusion has rewarded the conventional method of the pathologist, that perhaps a somewhat different presentation may prove at least novel and perhaps eventually more fruitful.

Our arrival at this conclusion was in no sense the result of any peculiar ingeniousness, but of simple chance. There came to hand a series of cases in which the essential anatomical material was available and in which the clinical aspects of the course of the disease had been followed for considerable periods of time. These observations had been made by one individual and were therefore homogeneous, a requirement not often found in large collections of clinical material. Moreover the Clinician had a profound, perhaps even exaggerated respect for the value of morphology as a basis for understanding disease. This, too, is a condition which does not always prevail. And for this reason there had been included in the armamentarium of his method, a technic designed to read as best it could the morphological changes which were occurring in the diseased kidney.

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* J. O.

Now it is obvious that such clinical observations can be truly correlated with anatomical observations, the term "correlation" being used in its proper sense and not with the facile meaning that one frequently finds in the treatment of biological problems. For as far as our actual knowledge goes and leaving the current Ossa-upon-Pelion-like heaping of hypothesis on assumption aside, there can be no more justification for attempts at correlation of most "functional tests" of the kidney with any morphological change as it is found at autopsy, than in correlating either aspect of the problem with sun spot cycles.

Never before, to our knowledge, has the pathologist ever had clinical observations which lent themselves to correlation with his findings in any but a casual meaning of the word. The opportunity that presents itself is therefore unique, and in it lies the purpose and value of his work in the present investigation; he is to observe what he can, describe his observations as objectively as possible and not add confusion to the general aspect of the problem, from which alone a solution can ever come, by originalities of his own. The "correlation" will then operate of itself, a result of the nature of the material at hand rather than of the art of the investigator. A humbler position than that often assumed by the Pathologist, no doubt, but one which he may fill with sufficient dignity.

Since correlation is the chief end of our study let us consider the two aspects of the problem of the renal lesion in Bright's disease as they are emphasized by the clinical author. We have first to describe the *nature* of the lesion that we find at postmortem examination. In a general sense this should not be difficult. The inflammatory reactions, whether "acute" or "chronic," can be noted and their distribution through the renal tissue followed. On the other hand degenerative processes affecting the tubular-epithelial elements may be observed, and lesions in the interstitial tissue or in the vessels of the kidney are easily determined. The amount of these various changes must, however, be estimated in at least a relative sense, for since all are found in a single example of the disease the simple statement of their presence may be entirely deceiving as to the general importance of the processes as a whole. And here with the appearance of quantitative values which demand expression the difficulties of the Pathologist begin.

In the second aspect of our problem, the *extent* of the renal lesion, these difficulties are enormously increased, for it is purely a quantitative question. "How much" can be only answered meaningly by "so much," and this we are frank to admit we cannot do with the objective clarity that our clinical co-worker has achieved. There has been, we would state, a constant pressure on his part, and an equally constant resistance on ours, towards the developing of some quantitative method for the expression of our morphological observations. We believe that even yet he feels, as others may, that we have missed an opportunity for the development of a novel and promising attack on a problem which has resisted the well-tried methods of the morphologist, and for this reason we feel that we must explain our rather backward-looking attitude in the matter.

The counting of various units of kidney structure or the measurement of their size would seem a possible procedure by the morphologist as he studies a section of the diseased organ. The first objection to this method would be the difficulty of a proper sampling of lesions whose distribution is peculiarly irregular, as they are in the kidney of a typical chronic Bright's disease. Large areas comparatively free of lesion alternate with similar areas which are severely involved. Possibly some laborious procedure could circumvent this difficulty but a chief, and to our mind, ineluctable obstacle would remain. We would be concerned in any such procedure with what is essentially a correlation, the counting of some anatomical unit as present or absent in a functioning sense, so that we would be falling into the error which we have just deprecated of attempting a pseudo-correlation of the two separate characteristics, morphology and function, concerning whose actual relations we know little or nothing.

A specific example will make our meaning clearer. Under very special conditions some such attempt may be justified. In a normal kidney, that is one whose function may be considered qualitatively constant, we have in an earlier study[34] compared the increase in the morphological entities, size and number of tubules and glomeruli, with that increase in the total function of these units which had resulted from a hypertrophy compensatory to the removal of one kidney. The close agreement obtained seems to confirm the validity of such a method.

It would be an entirely different matter, however, to apply the same method to an abnormal kidney. In such, both function and morphology vary not only quantitatively but also qualitatively, using the latter in a general sense, and no one has any certain idea as to the nature and effect of these qualitative variations in either entity. If we were counting, for example, the abnormally inflamed glomeruli of a kidney in an attempt to correlate this change with some measured functional variation, for instance, the amount of water excreted, should a certain glomerulus be considered less permeable on account of the thickening of its capillaries or less dense because of the disruption of its tuft? Or a tubule whose epithelial cells show a cloudy swelling may be "functioning" as well or even better than its normal neighbor for all we know, for it has been suggested, with some degree of justification, that cloudy swelling, though a degenerative process, is an evidence of cellular hyperactivity. These examples which we have selected are based in their turn of course only on assumptions, namely, that the glomerulus filters water and that the tubules secrete something. We believe they do, for the preponderance of evidence supports such a view, but we would not care to establish numerical statistics on the probability that would in their turn serve as a precarious basis for further hypothesis.

There remains, then, the semi-quantitative method of "grades" of involvement, such as I, II and III, which might be used. Although such a method may be necessary where observations are gathered by a large group of observers in order for some degree of homogeneity of data to exist, this makeshift is fortunately not needed in our work where the observations were made by the same individual. Though perhaps more impressive to some than the objectives, "little," "considerable" or "much" which appear through our descriptions, the numerals I, II, or III have exactly the same and no more real significance than the general terms we have used, and moreover they have the very serious disadvantage of casting a false sense of numerical accuracy into the problem which has no existence in fact.

We have therefore made little effort to be "quantitative" in our anatomical study for we feel that such an attempt in our problem would be not only full of the errors common to all statistical methods, but also of error of the most pernicious sort, that is, error of basic assumption bolstered up by an impressive adjunct of falsely quantitative expression.

Technic of the Pathological Methods

The technic of our pathological methods may be briefly described for it is the simple one with which everyone is familiar. The kidneys were obtained as soon after death as possible. When permission for an autopsy could be obtained a complete postmortem examination was performed, but unfortunately this was not always the case. Many of the patients died in the country and the kidneys alone were removed by the local attending physician and forwarded to us in a 10 per cent solution of formalin. Since our problem has been limited strictly to the renal lesion in Bright's disease these partial postmortem examinations were not the serious handicap that they would have been if a broader view of the disease had been under consideration. In many instances the body had been embalmed before the removal of the organs, and though this procedure destroyed to some degree the normal color of the gross specimen, this drawback was more than compensated by the excellent penetration of the tissues by the fixing fluid.

After the kidneys had been measured and the description of their gross appearance recorded, pieces were removed for microscopical examination. Supplementary blocks were also taken if the distribution of the lesion throughout the kidney was not uniform and special pieces were excised in many cases through the pyramids alone in order to study the large renal failure casts in the ducts of Bellini.

These blocks were placed in 10 per cent solution of formalin, in Orth's fluid and in Zenker's solution. The latter fluids were used even when the embalming of the body with formalin solution had previously fixed the kidney tissue, as this treatment improves the reaction of the tissues to certain staining methods. Frozen sections were then prepared and stained with Delafield's hematoxylin and Sudan III to show fat. Blocks were embedded in paraffin and sections stained by three routine methods, hematoxylin and eosine, hematoxylin and Van Gieson's mixture and Mallory's connective tissue stain.

In the actual study of the anatomical material an attempt at independent judgment on the part of the morphologist was made by his describing the pathological lesions without access to any of the essential clinical observations. In particular, reference was not made to the nature of the urinary sediment before the details of his microscopical examination had been recorded.

A problem of even greater difficulty than that of the actual observation of the lesions in the anatomical material has been their presentation. It has been our wish to give first in some detail the facts of our findings without any general or theoretical comment and in such an objective way that the reader will feel that he is sharing in the study of the actual material. Our hope is that he can then take these facts which he has gathered in a certain sense for himself, though perforce through our presentation, and use them for a useful criticism of our conclusions in the matter. The latter, as will be noted, have been relegated to a minor and definitely circumscribed section of their own.

Such an ideal, though simply stated, is of course impossible of attainment. The descriptive paragraphs of the text fail by far in the attempt; if detail is striven for, they become so lengthy and tiring that they cannot be read, while a cursory treatment leaves the reader with no visual picture of the processes at all. It will be noticed in reading each group of observations, that the same phrases and clichés are repeated again and again and this in spite of some care on the part of the writer to make the protocols individual. One would imagine that each member of a group was a duplicate of the other. In fact, though there is a general sort of familial resemblance between the case of any one group, their individuality is striking. After repeated study of the sections the writer can recognize Mc V. by the histological appearance of his kidneys as accurately as ever one could by the lineaments of his features.

Our main effort, therefore, has been devoted to an attempt at adequate graphic illustration, and this explains the rather elaborate nature of this part of our presentation. The plates are not to be considered illustrations however; they do not "illustrate" and were not chosen to elucidate the text, but rather the text supplements in its insufficient way the actual images, as near as may be, which we had before us in our study.

Photomicrographs, though often lacking in detail and visual contrast, are strictly objective and have therefore been chosen as our first exhibit in evidence. Every case, with no selective or convenient omissions, is presented in two manners. First, a very low power photograph of 20 times magnification which gives a view of a considerable area (2.8 sq. cm.) of the kidney. The entire breadth of the cortex and a portion of the medulla is thus included. At first glance, the reader, doubtless accustomed to a delineation of detail, may see very little in these photographs. They are however, to our mind, of equal if not greater value than the representations at greater magnification, for they show the extent to which the kidney was involved by the various processes. They have, therefore, a certain quantitative value and moreover the large areas which they cover preclude any subjective selection of samples in our presentation of the lesion, for the camera never lies more glibly than in its representation of a restricted high power field chosen from a fortunately selected region of a diseased process. These values in the low power photograph are well brought out if one contrasts the illustrations of a case of degenerative Bright's disease, where the architecture of the kidney is almost perfectly preserved (Plate XLVII A) with one of the terminal hemorrhagic type, where the structure of the entire kidney has been torn down, as it were, and reconstructed in an apparently planless fashion (Plate XXX A).

Beside this general view of the lesion in the kidney each case also has an illustration at the higher magnification of 125 times. Even here the field covered is considerably larger than that usually shown in illustrations of renal lesions, since several glomeruli and their neighboring structures are shown instead of the single tuft of the conventional illustration. This extension of the field in the photograph, along with the requirement of the presentation of every case, has caused considerable technical difficulties in the preparation of the photographs. We have preferred however to sacrifice esthetic values in some instances to our attempt at universal and general representation.

In these figures are shown the details of the processes whose general extent and distribution were previously represented in the low power picture. Although no "selection" was possible in the latter case, these higher powers with their correspondingly small fields must be chosen from restricted areas of the kidney section. The reader must therefore accept as adequate our care to make them as fair a sample of the lesion as a whole as is possible and one that will show to the best average degree the processes which are occurring throughout the kidney. In any case reference to the low power picture will serve as a check on their representativeness.

Before leaving the discussion of these photographs we would emphasize an obvious feature, but one whose value may be overlooked, and that is the fact that they are all taken at the same magnification of 20 and 125 times. The relative size of various structures in the figures is therefore identical in all cases. Some striking features may be brought out by a comparison of the plates of different cases, even better in fact that in comparison of the actual slides which cannot be before the eye at the same moment. For example, a comparison of the greatly enlarged glomeruli in Plate X B with the normal sized ones of Plate XLVII B or the shrunken tufts of Plate VI B. A comparative study of these illustrations is urged, of individual caseswith in each group and of one group with another.

We finally come to the drawings of the lesions, chiefly of high power which are grouped together and apart from the series of cases. That they are the work of Mr. Alfred Feinberg speaks sufficiently of their scientific accuracy and artistic merit. They are frankly "selected" specimens chosen, not from successive cases necessarily, but with the conventional idea of "illustrating" in the best manner what we have described in the text. They are grouped for convenience under the headings used in the presentation of the clinical and pathological data, and are to be referred to only as an aid to the reader in an understanding of our descriptive text.

We have dealt at some length on these features of our pathological work because to our mind it is the part which is of most value. We have endeavored to give the reader first not what we think of the renal lesion in a case of Bright's disease but an image of that lesion as we found it. He can then do his own thinking, which will be more stimulating to him and no doubt as valuable to the progress of general knowledge in the subject as the acceptance of the burden of our ratiocination.

The text of our descriptions needs little discussion beyond our previous statement of its inadequacy. A uniform method of presentation is used throughout. The general abnormalities found after death at autopsy are followed by a very brief description of the gross appearance of the kidneys. These may seem excessively condensed, but since the essential processes of the disease are visible so much more completely and at times only to microscopical examination, the importance of lengthy attempts at differential gross description seems doubtful. There then follows the microscopical examination, the lesions being discussed as they occur in the four main divisions of the kidney structure, glomeruli, tubules, interstitial tissue and arteries. Each case concludes with a short summary of the picture as a whole.

CHAPTER VI

PATHOLOGICAL DEFINITIONS

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Since in our introduction we have admitted that we have little new to add to the description of the pathological processes in Bright's disease, it might be assumed that the reader is familiar with the terminology and the nature of these lesions that have been described so many times and in such detail by past investigators. Nevertheless considerable uncertainty if not actual controversy prevails in many aspects of the subject so it will doubtless make for clearness if we define at least our interpretation of the meaning and significance of certain words and phrases which appear in our descriptive text.

CLOUDY SWELLING

Cloudy swelling as used in our descriptions refers to that parenchymatous degeneration of the epithelial elements in which changes of a granular nature appear in the protoplasm of the cell. Nuclear changes are as a rule not present, the cell is still living and the alteration in structure is apparently reversible. The lesion is therefore usually looked upon as the least severe of the various regressive processes that may affect the epithelium.

The granules which appear in the cell body are not of constant appearance or chemical nature. In what is apparently the mildest degree of the process they are so poorly defined that the protoplasm has only a diffuse ground-glass appearance, is swollen and stains more heavily than usual. It is in the more severe reactions that the granules become well defined and increase in size until in the end they may resemble droplets of some "colloid" material. Fahr, to whose excellent discussion of the entire matter[35] the reader is referred, has distinguished two stages of his nephrosis chiefly on the basis of these two types of cloudy swelling. (Plates LXXIII, LXXIV, LXXV, LXXVIII, LXXXV, XCIII, Fig. 13.)

* J. O.

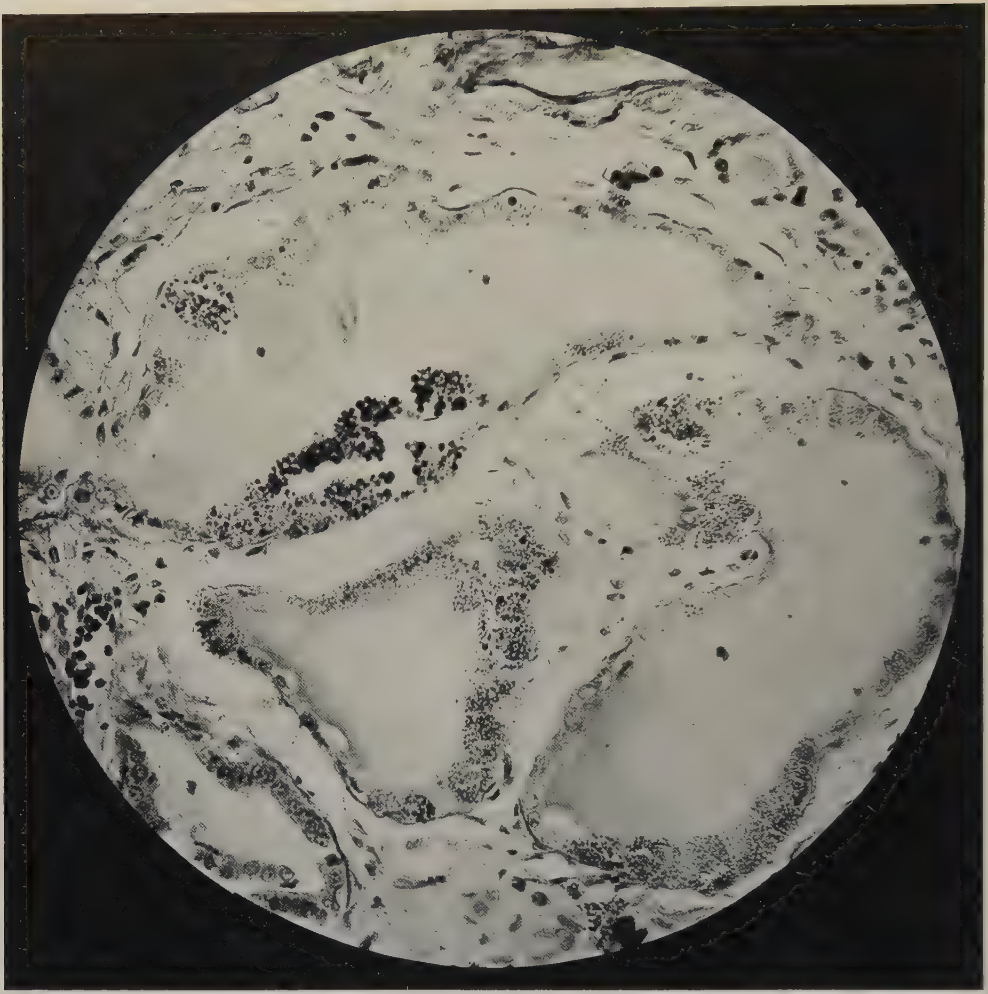

Fig. 13. Cloudy swelling with granules of both the small and large "droplet" form in adjacent tubules. The case is not one of degenerative Bright's disease where such findings are commonly described but is the terminal hemorrhagic form of Bright's disease. The section is stained by the Gram-Weigert method after fixation in Orth's fluid. The normal mitochondria do not stain under these conditions. These pathological granules are strongly gram positive.

The source of these granules is usually interpreted as the Altmann granules or mitochondria of the normal cell structure. There can be little doubt that many of the granular-droplet formations are derived from these preexisting elements by both morphological and, judging from changes in their staining reactions, chemical alterations. Another possible source should not be overlooked, however, and that is the occurrence of Albrecht's "tropfige Entmischung," a process which consists of a throwing out of the emulsion of the normal relatively homogeneous protoplasm of substances which take on under such conditions a granular-droplet form.

A certain localization of these processes is clearly apparent in the kidney. As Susuki has shown experimentally[30] and Fahr[35] has demonstrated in human kidneys it is the proximal convoluted tubule that is most susceptible to the change, although the broad ascending limb in Henle's loop is also frequently, and in cases of severe affection always, involved. The cells of the other tubules rarely show its presence.

The etiology of the condition has been well established by experimental studies. Many substances which reach the kidney through the blood stream may produce the lesion, such as metals, organic poisons of metabolic origin or bacterial "toxins." That the kidney excretes through and by its tissues these substances, along with the very likely probability that many of them are concentrated in the epithelial cells of the convoluted tubules either in the course of secretory or absorptive mechanisms acting in the tubules, is doubtless the reason why the kidney suffers so severely from the presence of any abnormal product in the blood stream. On the other hand abnormalities in the quantitative relations of the constituents of the blood stream without the presence of qualitative abnormalities may also, at least experimentally, effect this change.

Since the reaction to all these various toxic substances is essentially the same, it is impossible to distinguish by morphological study the exact nature of the intoxication. In our series it will be noted that the lesion in one group of Bright's disease is evidently the result of bacterial toxins, in another it is of definitely non-bacterial nature and in the third nothing is known of the etiological factor. In the latter, in fact, the presence of a "toxin" is only assumed by analogy, and in all three groups the processes are the same as far as the cloudy swelling of the epithelium is concerned.

Very little is known of the functional state of epithelium affected by this abnormality. Many have claimed that the milder type of the lesion at least is an evidence of hyperactivity on the part of the cells, for the response to heightened normal renal activity is accompanied by similar changes in the mitochondrial apparatus.[36] Fahr admits this possibility, but insists that the more severe type of granular degeneration, the characteristic of his nephrosis of stage II, is distinctly a degeneration in the strict sense of the word, that is, that there is a loss in degree of cell activity. Neither of these functional interpretations of anatomical appearances has much objective evidence to support it. Both are possibilities, and might be left as such if this speculation did not raise two important questions which must be considered, one of an immediate practical nature and the other of theoretical interest.

In regard to the first question, as we have previously pointed out, this ignorance as to whether the lesion produces, or is accompanied by, a decrease or increase in the function of the cell, or perhaps by both alterations at the same time in the kidney as a whole, precludes the use of any quantitative method by the morphologist if such quantitative data are intended for correlation with functional activity.

The second point, in whose fascinating subtleties we do not intend to be enmeshed at the present time, is that, as Aschoff has suggested, if the lesion is an evidence of hyperactivity on the part of the cell, then since it is an active response to an irritation, may the process not be considered, in a modified sense at least, an example of Virchow's "parenchymatous" inflammation? The results of such a conclusion must be considered, but are reserved for a later section devoted to theoretical speculation.

Fatty Degeneration

This is a similar degenerative process but distinguished by the accummulation of fat droplets in the protoplasm of the cells. The droplets may be minute, appearing like granules, or of considerable size. The nucleus is well preserved and the process may be considered reversible. Not only do the droplets vary in size; their chemical nature may vary, for in some instances they are composed of the isotropic simpler fats, and in others of the double refractive more complex lipoids. Both sorts of fat have been found in the fatty degeneration occurring in our series of cases without our being able to attach any especial significance to the occurrence of either type. The source of the fat is still a matter of some uncertainty. If the fat comes from outside the degenerating cell, and most of the evidence supports this idea, then the occurrence of either type of fat, isotropic or double refractive, may not be determined by the *renal* lesion in Bright's disease, but by disturbances in the lipoid content of the blood. This may explain why our study, limited as it is to the renal lesion, has found no especial significance in the chemical nature of the fat occurring in the process of fatty degeneration.

The distribution of the process in the epithelial elements is very similar to that of cloudy swelling, the convoluted tubule and the broad ascending limb of Henle's loop being most susceptible, and the straight tubules more resistant. The process is very apt to occur in cells whose structure was previously abnormal, such as the groups and clusters of atypical epithelium which represent collapsed tubules or in the regenerated epithelium which has replaced with its atypical structure the destroyed lining of the tubules. The prominence of this degenerative process under these conditions, as contrasted with the relative absence of cloudy swelling in such abnormal cells, is perhaps explained by differences in the causes of the lesion. For the same reason, fatty degeneration is not specifically limited to epithelial structures, but is observed in endothelial cells, leucocytes and fibroblasts. It is commonly observed therefore in the glomeruli at all stages of their inflammatory involvement and in proliferated connective tissue, even when the latter is completely fibrous or even hyaline.

The etiology of the condition is in part similar to that of cloudy swelling. Experimental study has demonstrated a long list of toxic substances which produce the lesion when they reach the kidney by the blood stream. As in the case of cloudy swelling the lesion was encountered in our cases even where the nature of the toxic substances was unknown and it is presumable that alterations in the blood constituents, especially of the lipoidal substances such as the cholesterol bodies, may be responsible in part at least for its development. There is another more definite etiological factor in the case however, which accounts for its distribution in both epithelial and the other elements we have just described. Anoxemia is a well-established cause for fatty degeneration, and there seems no doubt that through asphyxiation, local conditions, the result of the general effects of the disease processes in the organ, may play an important role in its causation. Local inflammatory changes, capillary thrombosis and fibrosis, by their interference with blood supply are examples where the cause of the fatty change need not be sought for in any abnormality in the circulating blood.

In the case of fatty degeneration again, we know nothing definite of its effect on cellular function. The process is frequently looked upon as being a more severe reaction and evidence of more damage to the cell's function than the occurrence of cloudy swelling. The fact that such an accumulation of fat in epithelial cells is a normal process in the kidneys of many animals shows the temerity of any such definite conclusion.

NECROSIS

Necrosis in the kidney epithelium has little of peculiarity as far as its morphological features are concerned that we need to discuss. The nuclear changes, whether ante mortem or post mortem, of pyknosis, caryorrhexis or caryolysis may all be observed in the cross section of a single tubule. The protoplasm of the dead epithelial cell is swollen and apparently coagulated, and as a result desquamation of the cell occurs. These cells may lie in the tubule lumen for some time with their altered structure still preserved, the nuclear changes still present and even the evidence of the earlier stages of necrobiosis, such as cloudy swelling or fatty degeneration, still apparent. Eventually they may disintegrate to form a granular debris which forms a constituent of tubular casts, though the occurrence of some cells intact in the terminal collecting ducts of Bellini show that many reach the bladder in some degree still recognizable. (Plate LXXVI.)

As in the case of the degenerative processes previously described, it is the convoluted tubule and the broad ascending limb of Henle's loop which is as a rule most severely affected. The straight tubules and especially the collecting tubules withstand most remarkably the toxic substances which are concerned in the causation of the lesion.

Here again we are in the dark as to the ultimate effect of this process on the activity of the kidney. To be sure we can feel certain that the activity of a dead epithelial cell is nil, but the effect on the function of the kidney as a whole may be an entirely different matter. And this is because recent evidence indicates a sharp distinction, one might say antithesis, between *cellular* function and *tubular* function. In a very simple case, where conditions were indeed simple enough to allow a reasonable certainty of interpretation, we have shown that damage to the tubule cells caused the kidney to excrete more effectively not only water and salts but also urea and phthalein.[37] The reader is referred to these studies where it is shown that this apparent paradox is the result of a depression of the normal absorptive function of the tubule cells, and that from this results a "catharsis" of certain substances which are normally removed to a greater or less degree from the urine as it passes down the lumen of the tubule. It is perhaps needless to insist again on our disclination to correlate under complex abnormal conditions function and morphology in the complicated human kidney. We have confined our efforts along this line to the relatively simple kidneys of frogs under carefully controlled conditions of damage, and though to our mind some success was achieved, as the reader may find by a perusal of the literature one can hardly claim a unanimity of expert opinion even in this restricted field.[38]

Necrosis also occurs in other than epithelial structures in Bright's disease. In the glomerulus, both as a result apparently of the passage of toxic substances through its capillaries or as the effect of the obliteration of the circulation in its tuft, necrosis results. Inflammatory lesions by the production of capillary thrombosis often produce this effect as do the vascular obliterations caused by the later proliferative changes of the inflammatory process or by sclerotic changes in the vessels.

Atrophy of the Epithelium

Atrophic changes in the epithelial elements of the kidney in Bright's disease are of such frequent and widespread occurrence that they warrant a somewhat more detailed consideration than can be conveniently given in the course of our descriptive text. The cause of these atrophic changes is largely the result of proliferative processes which occur in the later stages of all types of the disease. This development of connective tissue in the interstitial framework of the kidney or in the glomeruli may produce varying results. For example, a tubule enclosed within a fibrosing area may be directly compressed by the contracting tissue and in this way distorted in such a manner that its cross section assumes almost any shape. Its lumen is thus reduced to an irregular channel, which ultimately may be entirely obliterated. During this process the cells decrease in size, their protoplasm becomes scanty and stains more heavily. The nuclei are as a rule relatively somewhat less reduced and are therefore prominent, especially so since they are hyperchromatic from the condensation of their chromatin. (Plates LXXXI, LXXXII, LXXXVI, XCI, XCII, XCVII.) When the lumen is completely obliterated the epithelial cells form a solid cord rather than a tubule and as the membrana propria becomes blended with the surrounding connective tissue, the cross section of such a structure takes on the appearance of an irregular cluster or nest of cells. Though usually such cells are small, there not infrequently occurs in their protoplasm an infiltration with fat droplets and they then appear like fat-laden histiocytes. What part disturbances of nutrition, the result of the shutting off of the cells by the developing connective tissue from capillaries, play in the causation of these changes is difficult to say, though these are doubtless a factor not only in this late fatty change in the atrophied cells, but also in the entire course of the atrophic processes.

Another type of atrophy seen in the tubular epithelium is that which accompanies a cystic dilatation of the tubule. Such cyst formation frequently occurs throughout the cortex when connective tissue proliferation has occurred in its depths around the lower segments of the convoluted tubules. Obliteration at this point leads to stagnation of the secretion above, since the glomerulus and upper tubule may be relatively uninvolved and so continue to function. The resulting pressure may increase the diameter of the lumen many times and as a consequence the epithelium is reduced to a thin lining of low flattened cells whose deeply staining nuclei project above the level of the internuclear protoplasm. In the end the high cuboidal epithelium of the proximal convoluted tubule takes on the appearance of an endothelium. (Plate LXXXVI.)

Finally, if the glomerulus is obliterated by fibrosis the tubular portion of the renal unit may atrophy. This is usually interpreted as an inactivity atrophy, the assumption being that the tubule is unable to function without the aid of some substance, probably water, which is supplied to the secretion by the glomerulus.

Nothing is known of the functional ability of the atrophied renal cell. When the tubule lumen is destroyed the result is obvious, but whether the small shrunken cells of a still patent tubule function abnormally, is a conclusion which though reasonable is only an assumption.

Hypertrophy of the Epithelium

Since connective tissue proliferation in the interstitial framework of the kidney with resulting atrophy of the epithelial elements is rarely uniform throughout the cortex, scattered areas, often of considerable size, may be left more or less uninvolved by the pathological process. In them the convoluted tubules and their cells not only retain their normal size and proportions, but, when the destruction of functioning elements elsewhere has reached a considerable degree, may even increase in size. Such changes are commonly interpreted to be of a compensatory nature. Whatever the cause and nature of this hypertrophy, its degree is often remarkable. The cross section of the tubule may be twice that of the normal diameter and there is a corresponding increase in the size of the cells which line it. The normal proportion of cell to tubule is thus preserved, and there is little evidence as a rule of any significant increase in the number of the cells. Even in the constituents of the cell itself, such as the nucleus and brush border, this proportionate increase in size is seen. This hypertrophied epithelium is not however always entirely normal in a qualitative sense. Not infrequently degenerative processes are evident in it, such as cloudy swelling or fatty degeneration. (Plate XCVII.)

Our knowledge of the function of such cells is based on analogy with experimental procedures that produce changes which at least as far as their morphological aspects are concerned are of similar nature. We have already referred to the satisfactory correlation of the morphological and functional changes in compensatory hypertrophy following the removal of one kidney.[34] In this special case, however, the hypertrophy was a diffuse and evenly distributed process, and no regressive changes were present in the cellular elements, so that from this basis we can hardly speculate on what the effect of the focal bits of hypertrophied tissue, often involved in part at least by degenerative processes as they are seen in human Bright's disease may be on the function of the kidney as a whole.

The glomeruli in areas free of fibrosis also respond in the same manner with an increase in size. Near a group of hypertrophied tubules the associated glomerulus may be found with an enlarged tuft and an increased diameter of its capsule. Care must be taken, however, to distinguish other causes of glomerular enlargement which are entirely different in their nature. These are inflammatory engorgement or infiltration and cystic dilatation and will be discussed under a separate heading.

Regeneration of Tubular Epithelium

In a condition such as Bright's disease where for the course of years degenerative and destructive processes are occurring in the tubular epithelium, it is obvious that reparative processes must be of equally consistent occurrence if the organ is to survive. Evidence of such regenerative changes are seen in all forms of the disease.

Our understanding of regeneration in the kidney is derived chiefly from experimental investigations. It has been shown that after the destruction of the epithelial elements of the convoluted tubules and the broad ascending limbs of Henle's loop by various toxic substances, such as bichromate salts, corrosive sublimate, or uranium nitrate there soon occurs a proliferation of the remaining epithelium which has escaped the destructive action of the poison.[39] The cellular division is by both amitosis and caryocinesis. These new cells distribute themselves over the denuded membrana propria of the affected tubule, appearing in the early stages of the process as an atypical epithelial covering of either low, flat or cuboidal cells with excessively large, often oval and hyperchromatic nuclei. Later, beginning at about the end of the second week, these easily recognized new cells begin gradually to take on the appearance of the adult epithelium of the tubule and in the end cannot be distinguished from the original structures.

This perfect restitution of original structure does not always occur, however. If the toxic substance is one which produces damage or irritation to more than the epithelial elements of the kidney and results in the production of a condition resembling to a certain degree that of a chronic Bright's disease, an entirely different outcome is found. Uranium nitrate produces such a condition under experimental conditions and we have studied in some detail the course of the regenerative processes in the epithelium as the chronic "nephritis" develops.[36]

In the early stages of the reparative process the new-formed epithelial cells have the appearance of those just described. They are flat in shape with an irregular amount of protoplasm and their nuclei are large and oval in shape with an increased amount of chromatin. After the first few days, however, it can be noticed that the late changes in the appearance of the new cells already described do not occur. The cells remain immature, and even if the animal is killed months later the regions of new-formed epithelium are easily picked out by this peculiarity. Such tubules are lined by an irregular layer of epithelium, often several cells thick, whose oval nuclei show no orientation in regard to the axis of the tubule. The nuclei are also often excessive in number and may be heaped up to form giant-cell-like complexes which encroach on the lumen of the tubule by their uncontrolled proliferation. Even the intracellular organs, the mitochondrial apparatus which in the epithelium of the convoluted tubules is arranged normally in the definite structure of the batonnets, is profoundly altered. This granular material is scanty in amount in the new-formed immature cells and shows none of the complex arrangement into rod-like structures that is so typical of the adult cell. (Fig. 14.)

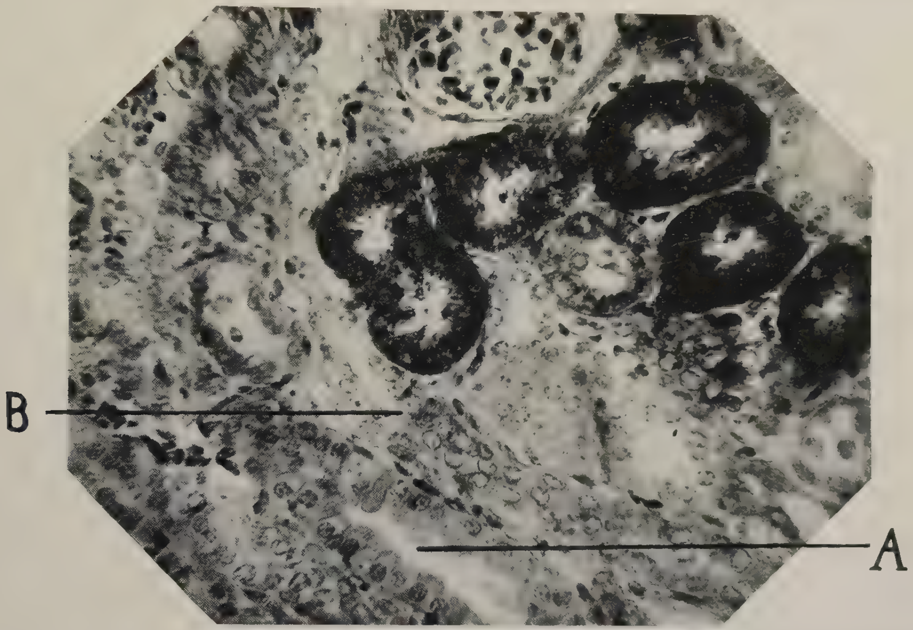

Fig. 14. The dark tubules in the upper right corner are original convoluted tubules filled with their deeply stained batonnets of Heidenhain. A is a normal collecting tubule in which the mitochondria are always scanty. B, and the tubules in upper left corner, are convoluted tubules lined with irregular immature regenerated epithelium. In them the mitochondria are reduced in amount and no batonnets are present.

Some factor has prevented this new-formed epithelium from attaining maturity. Although it has been suggested that the cause of this continued abnormality on the part of the developing cells might be sought in some toxic effect of the uranium on the germ plasm of the new cells, a condition analogous to the apparent effect of alcohol on developing germ cells, to us a more rational and simpler explanation seems to be an interference with their growth or nutrition by the proliferating connective tissue which is at the same time developing side by side with the epithelial structures. Such a proliferation of connective tissue is never found to any considerable extent as a result of damage to the kidney by bichromate or sublimate and in these lesions atypical regeneration does not occur. And as will be seen later atypical regeneration in the human kidney in the various forms of Bright's disease also seems limited to those instances where connective tissue proliferation accompanies epithelial damage and repair.

We are discussing the subject of regeneration in the kidney in Bright's disease at some length because it has not received much attention from past investigators. Oertel[40] has emphasized its importance and described the appearance found in different forms of the disease in some detail but since his work was done before the experimental study already mentioned, it is elucidated to some degree by findings of this other method.

In the cases of Bright's disease we have studied, essentially the same observations may be made as we have found in the experimental animals, so that morphologically the conditions are identical. In those human cases where connective tissue proliferation is slight or absent and which are therefore analogous to chromate and sublimate "nephritis" in animals, regenerated cells are difficult to recognize as such, for the majority of them have apparently assumed their adult appearance. Isolated groups of cells may be searched out, of course, in which the large oval hyperchromatic nuclei or the irregularly shaped protoplasm betray the cell as a newly formed one. Among the cases of cryptic degenerative Bright's disease are typical examples of these conditions. In kidneys where connective tissue proliferation has occurred however and which resemble in this regard at least uranium "nephritis" of animals, the cortex is filled with tubules which are lined with the obviously newly formed a typical regenerated cells. (Plates LXXVII, XCI, XCII.) As Oertel has described, giant cell-like heaps of cells and masses of unorientated hyperchromatic nuclei fill the irregular lumen of the tubule or low flattened almost endothelial-like cells are seen "creeping" over the denuded membrana propria. As might be expected in an organ which may have been the seat of a tearing down and building up process for years, often the majority of the convoluted tubules are lined with epithelium which "has never grown up."

These regenerated cells are of course vital and apparently healthy, and in a kidney of Bright's disease they may predominate in great numbers over those cells which show degenerative or regressive changes. How are we to estimate, judging from their morphological aspect, the function of the tubules of a kidney whose units are built up so atypically? The much vexed question of correlation whose embarrassing intrusion we seem unable to avoid.

Oertel has raised the same query in his consideration of these regenerating epithelial cells and has left the question open, but some advance has been made by the experimental method since he wrote. Ribbert, many years ago, first pointed out that the early regenerated cells of the kidney do not store up carmine granules when this substance is introduced into the blood stream of an animal in the same manner as do the original epithelial cells of the proximal convoluted tubule. Evidently there is some difference then in their behavior to this foreign substance. A more striking evidence that their function as well as their structure is abnormal is found, however, in our demonstration that they do not normally handle a substance which is peculiarly associated with the physiological purpose of the kidney.[36] Urea is not concentrated by the atypical regenerated epithelium that develops in uranium "nephritis" as it is by the normal cells of the convoluted tubules. This substance may be demonstrated in situ by microchemical means in the normal cells of the normal tubules in high concentration but in a section from a kidney with chronic uranium nephritis the atypically regenerated epithelial cells stand out in marked contrast by the relative absence of the reaction for urea in them, from their normal originally undamaged fellows (Fig. 15). The exact and ultimate significance of this fact is still unclear. Whether the urea is being secreted by the normal cells or absorbed from the lumen of the tubule is however beside the main point of our immediate interest. We think that we possibly erred in our original communication in assuming what then seemed the more likely, that is, that the urea is being "secreted" from the blood stream to the urine, but in whatever direction the urea is passing through the normal cells and being concentrated within them by the process, the process is not occurring in the atypical regenerated epithelial cells of the kidney in chronic uranium nephritis.

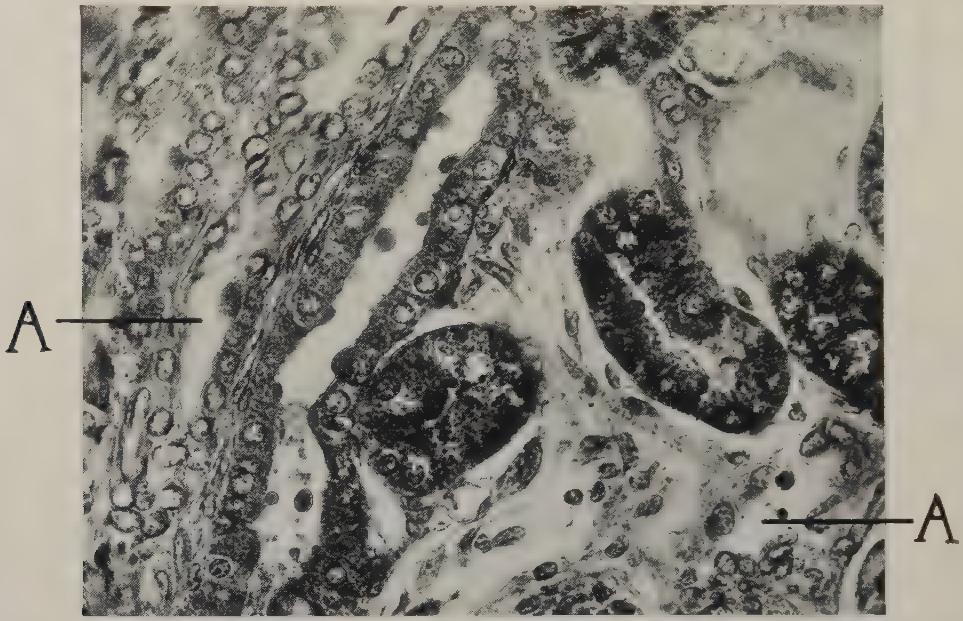

Fig. 15. Extending through the section is a longitudinal section of a convoluted tubule and to the right of it three cross sections of a similar portion of the renal unit, all of which are lined with their original normal epithelium. These cells are filled with dark deposits of urea. At *A* are other convoluted tubules which are lined with an immature regenerated epithelium. In these cells there is only a scanty deposit of urea precipitate.

By analogy, and it is a close one if we may use morphological criteria, we have strong cause for doubt that the atypical regenerated epithelium in chronic Bright's disease in man can handle urea in the normal manner. So again we see the futility of attempts by the morphologist in the present state of our knowledge at quantitative correlation of function and anatomy in a human kidney that is suffering from Bright's disease.

A final aspect of the question regarding the regenerated epithelium concerns the possible immunity of such cells to the effects of toxic substances which are harmful to the normal eipthelium of the kidney. Gil y Gil[41] has shown that the kidney withstands a second injection of uranium nitrate after recovery from a former uranium nephritis to a remarkable degree and MacNider[42] has demonstrated that such an immunity occurs only when the atypical type of epithelial regeneration has repaired the first injury. This, in conjunction with our conclusion concerning the function of these cells, might be explained by the not unreasonable assumption that their lack of function is the cause of their apparent immunity, since such cells may not concentrate the toxic substances within themselves as does a normally functioning epithelium. Such a conclusion is much more simple and direct than that the new cells have acquired some sort of immunity.

This matter has been emphasized because appearances noted in the atypically regenerated epithelium of the late forms of Bright's disease may be interpreted as evidence that the kidney withstands by some such mechanism the repeated attacks of the toxic agent which is the cause of the disease. Certainly in such a kidney one is often struck by the fact that the regenerated epithelium does not show regressive changes, such as the various degenerative processes or necrosis, to the degree that do those remnants of original kidney epithelium which are of the normal type. Unfortunately, both for the individual affected and for those who indulge in teleological interpretations of pathological processes, there is grave doubt that much is gained. Immunity gained at the expense of a vital function cannot be considered very advantageous. The importance to our mind of these phenomena is that they may account in part for the complexity of the picture seen in the kidney of Bright's disease, for though no purposeful result may be obtained, they certainly modify and complicate the reaction of the kidney tissues to a marked degree, and so help to explain why in this organ pathological processes are of such difficulty of interpretation.

TUBULAR CASTS

As has been mentioned previously in introduction, our morphological study of the renal lesion in Bright's disease is especially fortunate in that it has for correlation clinical data of a sort that have not been available before. Nowhere is this suitability better seen that in the study of the urinary sediment and in particular of the renal casts, for to them the particular attention of the Clinician was directed. That a correlation of these two aspects of the pathological processes involved will result in a useful concept of the disease is the hypothesis which forms the basis of the present work, but that such a possibility is not generally admitted is plain from the statement of Fahr who dismisses the matter as follows: "Aber man wird nur im sehr beschränktem Masse erwarten können, dass man aus der Art und Menge der Zilinder bestimte Rückschlüsse auf die Art und Schwere des Nierenleidens ziehen kann."[43] The Pathologist's chief contribution to the present work is the demonstration that the Clinician from the kind and number of the casts did draw very definite and remarkably accurate conclusions concerning the nature and degree of the renal affections which he studied by his special methods.

Before discussing the various sorts of casts found in situ in the kidney after death, we would call attention to one observation of the Clinician which is of importance in this regard. It was very definitely noticed by him that the type of cast found in the urine might change as the lesion in the kidney progressed. It follows, then, that it is quite possible for the casts found in situ in the kidney tubules to differ from those described in a sample of urine unless this sample was collected at a time fairly close to the individual's death. Another possible source of lack of exact correlation between the clinical and pathological observations lies in the fact that casts may be retained in the kidney or at least pass into the urine in so small numbers as to be found with difficulty if at all. Moreover conditions in the kidney, where the casts form, are the most favorable for their preservation, while conditions in the urine may be such as to destroy them completely. For example, plugs of various materials filling the tubule lumen which appear to be firmly consolidated into definite casts may, when free in the urine, disintegrate into their constituents and thus escape recognition. This seems to be the fate of a certain number of the blood casts to be described later and which were found so regularly in situ in the active stage of hemorrhagic Bright's disease. In spite of these facts, however, the reader will note a striking harmony between the type and number of casts found in the urine by the clinical examination and those found in the sections of the kidney after death. In certain cases, indeed, the theoretical expectations of the Clinician, who had not been able to find in the urine of a patient in the terminal phases of the process the particular type of cast which his experience with the earlier stages of the disease in the same individual had led him to suspect, received final confirmation from the morphologist, who was able to demonstrate the suspected casts still held within the kidney tubules. The Clinician's observations were identical therefore both in the purpose of their technic and in their interpretation with those of the Pathologist, an expression of unity of method which rarely obtains.

Our morphological observations showed little new in regard to the mechanism of the formation of these structures. Materials from both the glomeruli and the tubules, the product of degenerative changes in the latter and of inflammatory exudation in the former, contribute to their composition. This detritus may be observed in all stages of consolidation from loosely packed debris to firmly coagulated casts, in the literal sense of the word, of the tubule lumen. As a general rule the more perfectly formed casts are found in the lower levels of the tubule, though they may be present as such even in the upper divisions of the proximal convoluted tubules.

Hyaline casts seem to form in at least two ways. They may be the result of a hyalinization of casts which previously contained debris of various sorts and which were originally not optically homogeneous. This material apparently goes into solution and the appearance of the cast gradually assumes its typical transparent characteristic. Others, and perhaps the majority, are very definitely hyaline from the time of their origin, however, and are composed of a clear, coagulated and, as chemical examination has shown, altered protein. Epithelial cells, blood cells or leucocytes of various sorts may be adherent or even enclosed in the coagulated mass.

The source of the protein material which forms the substance of these casts is not clear, nor does its chemical similarity to amyloid aid us in the determination of the question, since we know little of the origin of this peculiar substance. Some have suggested that it has its origin in a perverted activity of the tubular epithelium. Extrusion of droplets of semifluid substance from these cells has been described. It has been suggested that it may be derived from some product of degeneration of these cells, for the latter contain gram-positive granules which may be traced to the lumen of the tubule as the cells disintegrate. This process is correlated with the gram-positive reaction of the hyaline casts.*

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* The application by Lichtwitz[44] of the theories of colloidal behavior to the formation of casts remains unfortunately in the stage of hypothesis, though there can be little doubt that the phenomena, such as the coagulation of protein materials, which occur in their formation are controlled by these mechanisms.

Various elements may remain in the compact and fully formed cast in a form which still allows their identification. In this manner arise epithelial casts, while finely divided debris is the characteristic component of the granular cast. Fatty droplets, of either isotropic or anisotropic properties, derived from the disintegration of epithelial cells in which has occurred a fatty degeneration, or extruded as such from the glomerular tuft where this process also occurs, are embedded in or are adherent to casts of the granular or hyaline type and so form the fatty casts. Under experimental conditions at least fat, if present in high concentration in the blood stream, may pass through the intact glomerulus, so that its presence either in the form of free droplets in urine or adherent to casts is not necessarily indicative of any lesion in the kidney. Leucocytes, especially polymorphonuclears, may also be enclosed in these formations and due to the proper histological fixation of the tissues are often more easily identified than when they are studied in the urinary sediment.

The formation of the blood casts, whose importance has been emphasized by the clinical author, may be followed through all the stages of their development. The source of the red blood cells is the glomerulus and from here too is furnished the other essential component of coagulable protein, probably fibrinogen, which cements them to a definite coagulated mass. Red cells may be found, still apparently discrete judging from their loose arrangement and perfect preservation, lying in the group of cross sections of a single convoluted tubule which lies in the neighborhood of the glomerulus into whose capsular space they were shed. (Plate LXXXVIII.) In other sections of the tubules, the red cells though still well preserved are included within a coagulated matrix, and from this stage on, the gradual dissolution of the blood corpuscles may be followed until casts are found which can be identified only by the presence of the typically golden brown blood pigment or by the peculiar color of their reaction to the eosine stain. (Fig. 16.) A microchemical reaction, discovered by chance, often aids in their recognition if the tissue has been fixed in formalin. This fixative forms an insoluble black precipitate with hemoglobin which is easily distinguished from any real pigment. The true significance of certain casts has been made out by these means where the ordinary methods of examination disclosed no evidence that the object was a blood cast.

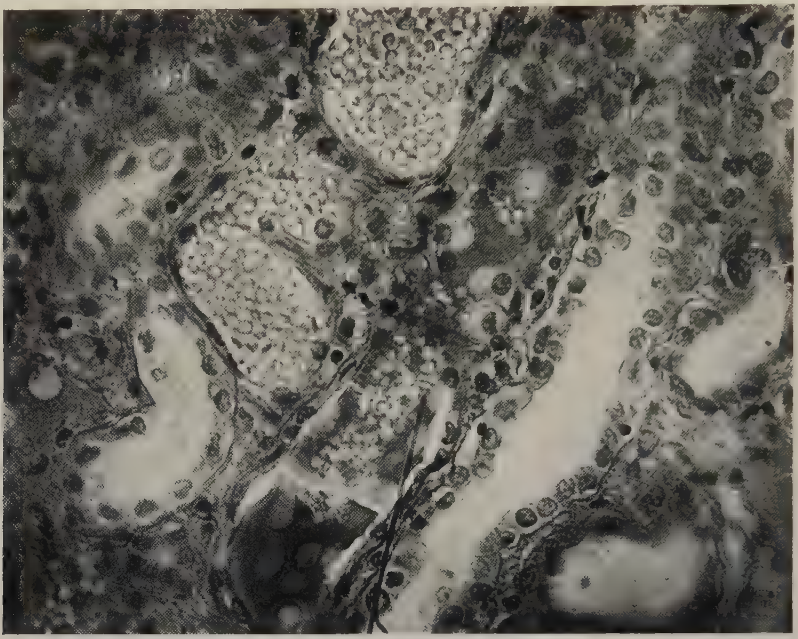

FIG. 16. In the three upper tubules freshly shed discrete red blood cells may be seen. In the tubule cut in longitudinal section, which the pointer indicates, red cells are seen incorporated by coagulated material into a blood cast.

From the clinical standpoint the blood cast is of especial importance for largely upon it rests the recognition of that form of kidney lesion which has been designated as hemorrhagic Bright's disease. It is of importance therefore to emphasize those essential features of its formation as they are revealed by the study of its actual formation in the tissues which account for its peculiar significance. The two essential requirements, as we have already stated, are first red blood cells and second, a cementing substance to bind the cells together and form the matrix of the cast. These two components must also be furnished at approximately the same time, for the true blood cast is not a hyaline or granular cast on whose surface an occasional red cell is adherent, but one which is throughout its structure a mixture of red cells and cementing substance. The only process which affords these three requirements with any regularity is an exudative inflammatory process in the glomerular tuft, for by such red blood cells and a fibrinous coagulable exudate are poured out into the tubule. In many other conditions the glomerular tuft is sufficiently damaged so that red blood cells may escape, but without the other essentials of blood cast formation, they remain discrete and appear in the urine as such. Excessive and violent exercise alone may produce such a condition. Hemorrhages into the capsular space are also not uncommonly seen in other forms of Bright's disease. The presence of bile pigments in the blood and urine which produce degenerative changes in the epithelium as well as glomerular hemorrhage is an example of only partial fulfillment of the necessary conditions of blood cast formation, as are also those diseases where associated with glomerular bleeding are found definitely inflammatory lesions in parts of the kidney other than the glomeruli, such as in the degenerative Bright's disease of the pyogenic type which is associated with amyloid. Judging then from the appearance of the blood casts as they are observed in situ in the process of formation, an exudative hemorrhagic glomerulitis is the only pathological lesion which produces them in significant numbers and in their characteristic form.

The large broad renal failure casts also require some especial mention, since the reason for and the mechanism of their formation is shown by morphological studies of the kidney. They have been found regularly in situ in the kidney in those cases in which they were found in the urine. Their size is explained by the site of their formation, which is the terminal dilatation of the ducts of Bellini, just at their point of entry into the pelvis of the kidney. For this reason a section for their demonstration should pass at right angles to the surface of a pyramid as it protrudes into the calyx, and then only a short and occasional section will properly display the contained cast because of the angle which the duct makes as it enters the pelvis.

This terminal part of the collecting tubule is found packed with detritus which differs strikingly from the casts of the tubule lumen found higher up in the renal unit (Fig. 17). The material is composed of blocks and irregular masses of granular or hyaline debris, including within them and between them remnants of dead cells and leucocytes. Very frequently there is a hyperplasia of the epithelium of the collecting tubule in this region with desquamation, and these cells are added to the mixed content of the cast. This proliferation is of course not peculiar to disease of the kidney, and may be seen in kidneys which are essentially normal, but its occurrence in the kidney in the terminal stage of Bright's disease seems to help in the formation of these casts. The other characteristic of the broad casts, their fragility, is easily made out. There seems to be little cementing substance to bind the various materials together, a striking characteristic of the smaller casts of the ordinary type found in higher levels of the tubule, so that even in the histological sections they are observed to be breaking up into irregular fragments. When the terminal exit of the duct of Bellini is plugged by such a broad cast the material may back up into the higher levels of the collecting tubule for a considerable distance into the medulla. In this way similar casts but of smaller diameter may be formed, and their recognition, both in the kidney and in the urine, then depends on their peculiarly mixed and loosely knit structure. (Plates LXXXVII, XCVIII.)

Judging therefore from the appearance of these casts in the process of formation, they may be interpreted as loose packings of the terminal ducts with heterogenous debris the origin of which is any portion of the upper

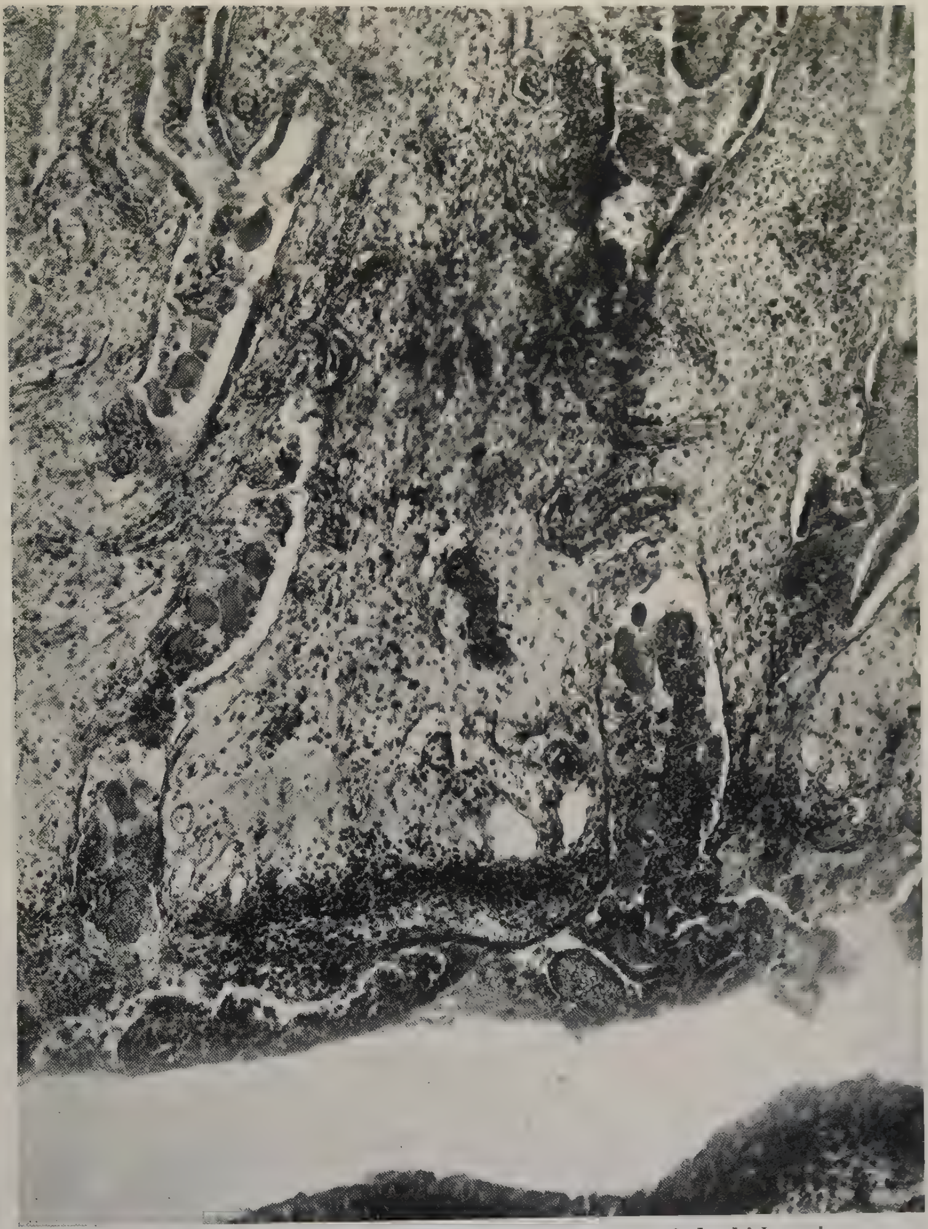

FIG. 17. Entrance of two ducts of Bellini into the pelvis of the kidney in a case of terminal hemorrhagic Bright's disease. They are filled with typical broad renal failure casts, which show their fragile and mixed structure. (Cf. XLIII A and B.)

tubule. That they are forming in a portion of the tubule where no significant lesions are in operation is perhaps the reason they do not contain those substances which ordinarily cement debris to a firm well-made cast. Such materials have coagulated or lost their adhesiveness long before reaching this portion of the tubule. The conditions in this regard are therefore strikingly different from those which exist at the seat of origin of the ordinary small cast.

Clinical observations have shown that the broad casts are most frequently found when only a moderate or small amount of urine is being excreted, or they are found in greatly increased numbers when a sudden output of urine follows a period of oliguria. This suggests that a lack of proper flushing of the duct may be the immediate cause of the collection of debris, and the appearances seen in the section fit closely with such an interpretation. Even their occurrence associated with a considerable excretion of water by the kidney as a whole, a diuresis in fact, is not incompatible with this hypothesis if one considers more closely the anatomical and pathological factors that are involved.

The duct of Bellini is the terminal and only drainage outlet of a considerable number of renal units. In the terminal stages of Bright's disease the normal architecture of the kidney has been almost entirely destroyed. Fibrosis has occluded glomeruli and obliterated tubules, and that these elements are not draining properly is obvious from the cystic dilatation of those that are found in the cortex of the kidney. Moreover these changes are strikingly irregular in their distribution so that some portions of cortex are left relatively uninvolved or may even show hypertrophic changes. This, in conjunction with the well-established principle that even the normal kidney does not function uniformly and synchronously in all its parts, will explain how a considerable amount of urine may be flowing from some of the terminal ducts of Bellini while from others the output of fluid, and consequent flushing of the lumen, may be very small. The appearance in the sections fits very well with such an interpretation, for as a rule not every duct of Bellini contains a broad cast, but only the occasional one.

The occurrence in histological sections of greatly dilated tubules, usually convoluted portions, which may be found in the cortex of kidneys involved in the fibrosis of late stages of Bright's disease and which are often filled with coagulated material, obviously bears no relation to the formation of the broad renal failure cast. The material in the lumen of these tubules has collected because its passage down the tubule was prevented by some obliteration of the lumen. These masses are not casts in the usual sense of the word, since they cannot reach the urine. (Plates XXII B, XXIX B, XXX B, LXXXVI.)

In concluding this consideration of cast formation in the kidney we would, with the indulgence of the reader who is doubtless weary of "classifications" in the subject of nephritis, point out that casts may be separated into two groups. One of these groups includes those casts which have specific characteristics other than their appearance, while the second includes less well-defined types of various origin and significance. In the first group are the hyaline casts, distinguished by the chemical nature of their substance; the blood casts, characterized and separated from all others by the nature and site of the inflammatory processes which afford the essential material for their formation, and the renal failure casts, whose formation is determined by the site of their origin and a condition of decreased function of the renal tissue. The other group of granular, epithelial, leucocytic and fatty casts has no such well-defined characteristics, so that its significance is less accurately determined. Nevertheless, all are indicative, as our morphological studies will show, of the pathological processes which are occurring in the kidney in different forms of Bright's disease.

Amyloid Degeneration

Little need be said of our observations on the occurrence of this form of "degeneration" in the kidney of Bright's disease, as we have nothing to add to previous studies of the condition. It is found in our series in those cases which have been grouped together as degenerative Bright's disease of pyogenic origin. All degrees of the process were present, from those where only small deposits were found in the glomerular tufts to those where all the glomeruli had been transformed to almost solid masses of the material and where large quantities were found along the straight vessels of the medulla. (Plate lxxix.)

The relation of the deposit in the kidney tissue to other processes found in Bright's disease may be briefly stated. Associated with its deposition around the finer vessels are found the characteristics of degenerative Bright's disease, namely the varied degenerations which affect the epithelial elements. These lesions are in certain cases more striking in appearance than the infiltrations with the amyloid, so that one gets the very definite impression that the infiltration with this substance is not the characteristic of any particular type of the disease, but merely a feature which may be added to the other more essential lesions.

Inflammatory processes are regularly encountered in kidneys thus affected but these are usually of a productive and proliferative type and apparently bear little relation to the amyloid itself. They are found in the interstitial tissue some distance from the amyloid deposits, and there is also relatively little evidence of inflammation in the glomeruli which may be heavily infiltrated with the substance. The amyloid has, then, little irritating effect on the kidney tissues, a fact confirmed by appearances seen when it is present in other tissues than the kidney.

The larger arteries of the kidney, in spite of this affection of the arterioles and capillaries, may show surprisingly little evidence of damage. They are as a rule normal, or show moderate proliferative changes in their walls as compared to those found in the later stages of other forms of Bright's disease. The significance of this fact will be considered in a later paragraph where arterial lesions in Bright's disease are discussed.

The glomeruli, as already mentioned, except for apparently passive effects such as increase in size from distention or obliteration of capillaries and atrophy of tuft cells seem to be little affected. In the end, however, the glomerulus may be entirely destroyed, consisting in fact of nothing but a solid clump of the hyaline material in which scattered atrophic cells remain.

Since the amyloid bears no immediate relation to either the degenerative lesions in the epithelium or to the inflammatory changes in the kidney framework but remains in the tissues as a relatively innocuous material, it would seem best, from the pathological standpoint at least, not to consider it the characteristic of any especial form of Bright's disease as has been done by some in the past. Pyogenic degenerative Bright's disease may exist with or without amyloid, and amyloid may be found as part of a generalized disease in kidneys which show none of the significant lesions of Bright's disease. It is therefore only one feature of the condition, as we have previously said, and not an essential one.

Tubular Obliteration and its Results

It is in the later stages of Bright's disease, in which the proliferative processes in the interstitial tissue have become extreme, that obliteration of tubules and its resulting effects are frequently seen. Apparently by pressure alone from the proliferating and contracting fibrous tissue the tubule may be so compressed that its lumen is destroyed. The epithelium thus enclosed atrophies, so that the cross section at such a point resembles the nest-like clusters of atypical cells which have previously been described in the discussion of atrophy. (Plates LXXXI, LXXXIII, LXXXVI, XCVI, XCVII.)

Obliteration of the tubular lumen from internal changes also occurs and may be the result of at least two processes. Debris of various sorts, either as such or in the form of casts, may plug the lumen and the pressure of these substances upon the epithelial cells can be recognized by their flattened and atrophied appearance. (Plates LXXXVI, XCVI.) Such processes play an important part in the late stages of certain forms of the experimental disease, and we have described the organization by fibrous tissue of such masses of detritus in uranium nephritis.[39] Susuki and Aschoff consider this irreparable obliteration of the tubule lumen and the resulting dilatation of the tubule above as analogous to what occurs in a hydronephrotic kidney. In this condition fibrosis also follows, so that they find in this factor of tubular obliteration the cause of the connective tissue proliferation which is characteristic of the later stages of uranium nephritis. Though similar processes occur in the human kidney in the later stages of Bright's disease, we doubt if these hydronephrotic factors can play the important part in the genesis of the connective tissue formation that they do not in the experimentally produced disease.

Finally an excessive regeneration and hyperplasia of the damaged epithelium, especially when these processes are associated with degenerative changes, may obliterate the lumen of the tubule with masses of living cells. (Plate XCI.)

The results of obliteration of a tubule depend largely on the functioning condition of its upper portion. If this too is enclosed in connective tissue or its lining epithelium has been destroyed and its glomerulus is the seat of a far-advanced inflammatory process, then no striking results may follow the obliteration of the lumen. Not uncommonly, however, these upper structures are more or less well preserved, at least as far as their ability to excrete fluid is concerned, and under these conditions the tubule dilates above the point of obstruction. The contained substance may be almost clear fluid or it may contain any amount of debris or inflammatory products. In either case the epithelium is flattened out by the contained pressure and atrophies until an equilibrium is attained and the dilated cyst-like tubule remains filled with a coagulated material which resembles colloid in its appearance. In the later stages of terminal hemorrhagic Bright's disease, where the architecture of the cortex is so profoundly modified, groups of such tubules are as a rule seen scattered through the cortex (Plate XXII A). The peculiar grouping of these spaces is the result of the section passing through the many closely clustered convolutions of a single tubule.

The glomerulus of such a tubule may also be similarly affected, and here again the result depends on the previous state of that structure. If its tuft is filled with inflammatory infiltration and its capsule with exudate or if the latter is obliterated by adhesions, no marked dilatation can occur. If it has been free of these adhesive and collapsing processes, however, dilatation of the capsule follows, the tuft collapses and atrophies and the whole glomerulus appears as a small cyst. Such cystic glomeruli are found particularly in the late stages of arteriosclerotic Bright's disease, for in such the glomeruli are less involved by inflammatory processes.

Both tubular and glomerular dilatation therefore share in the formation of the cysts which are so commonly found both on the free surface and in the cortex of contracted kidneys. For the reasons just mentioned they are particularly common in the late stages of arteriosclerotic Bright's disease, reaching in size by the fusion and coalescence of smaller cysts 1 or 2 cm. in diameter. Congenital cysts may also be present in such a kidney, and it is often difficult if not impossible to distinguish these structures from those which have arisen by the mechanisms just described.

INFLAMMATORY PROCESSES

Perhaps in no field of pathology has controversy waged more ardently and incessantly than in that which includes the nature and definition of inflammation. Virchow, Cohnheim, Weigert, Ribbert and so to Aschoff in the present day—a history of modern pathology may be found in the work of those who have engaged their talents in the complexities of this subject.

But even as a spectacle, the contest has perhaps begun to be exhausting, at least to the humbler followers of the controversy who with an increasing bewilderment have vainly struggled to and fro as the battle swept from one extreme of the lists to the other. As a result the term "inflammation" has assumed a neutral and indefinite meaning in the minds of many of us, defined in so general a sense that the need of more rigorous consideration often leaves us somewhat embarrassed.

From this comes a part at least of the confusion which is so prevalent in descriptions and classifications of Bright's disease, and so unfortunately for us, both writer and reader, we must attempt some explanation of what we mean when we say that inflammatory lesions are either present or not in a certain example of the disease. Such a definition will of course satisfy none but the writer, and him only for its immediate practical purpose. Even the general reader will point out its weakness and those to whom the matter is one of professional regard will doubtless vigorously object to the brevity and insufficiency of the summary treatment that we shall give the subject.

By inflammation we mean those exudative and proliferative processes only which are observed in the vascular and fixed tissue elements of a tissue which follow as a reaction to some irritative stimulus. Nothing is said as to whether the processes are active or passive, progressive or regressive. All teleological aspects of the matter are omitted. A "parenchymatous" inflammation cannot therefore be included within its limits nor can epithelial hyperplasia for though no strictly logical reasons exist for this exclusion, very practical advantages, as will appear later, result by such an arbitrary deletion of them from the concept of the inflammatory process. And with this brief statement those interested in the broader epistemological aspects of the subject are referred to Oertel's work,[40] where these matters are treated in some detail.

Our statement of how we are using the term in the present discussion needs very little elaboration. Acute inflammatory processes are those in which exudative changes predominate, such as hyperemia, edema and the extravasation of leucocytes and fibrinous exudate. In the chronic inflammations proliferative processes are characteristic, such as infiltration with round cells, proliferation of fixed tissue cells, especially of fibroblasts, and the formation of collagen. A subacute inflammation is one which lies midway between these two extremes and may show more or less of the characteristics of either type. There is often confusion as to whether these modifying adjectives refer to the nature of a process or concern more a time relation. As we use them the emphasis is on the description of the nature of the process. An acute inflammation may remain acute for considerable periods of time, and since chronic inflammations may be "chronic" from their origin, they too may be of short duration, though obviously from their lesser effects on the tissues they do not as a rule come to our attention until a considerable time after they have begun.

The relation of these different forms one to the other follows from what has just been said. The activity of an acute inflammation may die down, and, if the irritant continues in a lesser degree, be followed by a subacute or even chronic inflammatory process. The healing of the destructive results of an acute inflammation by connective tissue replacement is not, when it is completed at least, to be considered a chronic inflammation. Such an area is a "scar," a static condition of completion even though it may appear with its proliferated collagen and enclosed fixed tissue cells morphologically somewhat similar to the active process which characterizes the chronic inflammation.

In different parts of the kidney these inflammatory lesions are seen in different degrees. In the glomeruli the acute exudative processes may be particularly well developed, such as hyperemia of the tuft and the pouring out of an exudate which contains fibrinogen, polymorphonuclear leucocytes, and even red blood cells into the capsular space. In the interstitial tissue similar acute changes may occur, but from the different anatomical relations are somewhat modified. Hemorrhages and the deposit of fibrin are rarely seen, though hyperemia, edema and even polymorphonuclear exudation may be marked. Care should be taken to distinguish passive congestion in the kidney from an active hyperemia. The cause of such a congestion may be a general one, such as cardiac failure, or local, particularly in the later stages of chronic Bright's disease where relations have been distorted by connective tissue formation. The significance of such congestion in the development of the later stages of Bright's disease will be considered later.

Proliferative inflammatory changes occur in all parts of the organ. In the glomeruli the typical infiltration with "round cells," i.e. lymphocytes and plasma cells, may be present as well as proliferation of the fibroblasts and endothelial cells of the capillaries of the tuft. These changes are not limited to the tuft, but may extend out into the exudate of the capsular space and result in its organization. In the interstitial tissue of the kidney, throughout the cortex especially, the same infiltration with round cells and collagen formation by means of fibroblastic proliferation are pronounced in the late stages of most forms of chronic Bright's disease. Considerable variation is noted in the distribution of these productive inflammatory processes throughout the interstitial tissue of the kidney. What determines this variation in distribution is not clear, but its importance is of the greatest for on it depends to a considerable extent the future course of development of the disease.

In the majority of the cases of those who died in the active stage of hemorrhagic Bright's disease the inflammatory involvement of the kidney was a diffuse one. One part of the cortex was involved as much as another; every tubule was separated from its neighbor, each was compressed and atrophied to an equal degree and every glomerulus showed the effects of the involvement. On the other hand in the kidneys of those who died in the stage of a terminal hemorrhagic Bright's disease the inflammatory changes throughout the cortex were distinctly patchy in their distribution. Areas or clusters of tubules and even glomeruli were found still fairly well preserved lying on a background formed by atrophic parenchyma where the inflammatory fibrosis was more marked. As will appear later the diffuse type of distribution was found in individuals who died of kidney failure (uremia) while the disease was still in its earlier active stage, while those whose lesions were of the patchy type survived and passed into the terminal stage of the process, provided they did not succumb to some infection or arterial accident.*

A point of considerable interest and difficulty arises when we consider the fibrous connective tissue proliferation which is observed in the walls of the larger blood vessels and its relation to the inflammatory processes, but this we shall discuss in a later section.

Throughout the descriptions of the cases which follow, the phrase "no significant inflammatory lesions" will be constantly encountered. It is an expression for which we have no particular defense, except that we see no way for the avoidance of its disadvantages. What is or is not significant may be interpreted in a widely different manner, especially in a condition like Bright's disease where opinion plays such an important role. Those who feel that all Bright's disease is a "nephritis," will doubtless demur to the statement that any amount of inflammation no matter how slight may be considered insignificant. A definition therefore may be demanded of our use of significant. By insignificant we mean that a lesion is in our opinion so limited in situation, extent and activity as to bear no appreciable relation in either its anatomical or functional aspects to the origin, development or final outcome of the disease. The finding of a single group of a few round cells in the interstitial tissue of the kidney in a case of Bright's disease which is otherwise entirely degenerative in nature is, for example, considered insignificant by us. If we were to establish more strict criteria, every kidney obtained at autopsy would of necessity be considered as affected by Bright's disease, and all attempts at study of the condition would be thrown into a more impossible state of confusion than even now exists. There is in a certain sense an analogy between our problem in this matter and that of the Clinician, who found all the characteristics of Bright's disease in "normal" individuals, and was therefore forced to consider a certain degree of cast formation and albuminuria insignificant.

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* The terms patchy and diffuse as used here, referring to the type of inflammatory fibrotic destruction of the kidney parenchyma, bear no relation to and should not be confused with Volhard and Fahr's use of "focal" and "diffuse" to designate two different sorts of nephritis. A further discussion of this point will be found on page 592.

But we doubtless labor the point. There is no need in the present day to insist that disease is anything more than a disturbance of the average, and therefore normal, quantitative relations of function and structure or to point out that throughout the whole realm of medicine we are constantly forced to decide on what is so significantly altered as to be properly considered pathological. Moreover the practical use of the term, in separating different types of Bright's disease from each other, cannot be seriously opposed unless one wishes to accept the logical *sequitur* that there is but one form of the disease, for everyone from Virchow's time admits that the lesions in Bright's disease are both mixed in nature and diffuse in distribution. We have the choice then, from the pathologist's point of view at least, of considering all cases of the disease to be the same, or of picking out the significant lesion. The pragmatic method is obviously the only solution if we wish to advance our knowledge of the condition, and the lesions themselves, depicted as completely as possible both graphically and in our text, will, we hope, allow the reader to judge for himself whether we have used this method properly.

GLOMERULITIS

We have not used in our descriptions the term "glomerulonephritis" for this word includes within itself an expression not only of the lesion, inflammation of the glomeruli, but an opinion concerning the nature of the disease as a whole. The connotation of the term glomerulitis is limited to a description of the lesion and its site and is therefore preferred. Klebs,[45] Löhlein[46] and more recently Fahr have described the details of the inflammatory processes in the glomeruli. The latter for descriptive purposes divides the lesion into two types. In the intracapillary form, a term first used by Welch in 1886, the inflammatory lesions are more or less confined to the substance of the tuft. This is enlarged by hyperemia and at times edema, and by the accumulation within it of leucocytes. In the acute forms these are chiefly polymorphonuclears, while in the subacute types round cells, including lymphocytes and plasma cells, may predominate. (Plate LXXXIX.) Thrombosis of the capillaries of the tuft with fibrin thrombi and necrosis of portions of it may also occur. (Plate XCI.) The capsular space remains relatively free of exudate, though some inflammatory materials are apt to escape into it. The result of these changes is an enlargement of the tuft, a feature which may be quite striking. A comparison may be made of the glomeruli in Plate X B which show these lesions with those of Plate XLVII B where the glomeruli show no significant lesions.

In the subacute and chronic forms of the lesion proliferative processes are evidenced by the cellular infiltration of tuft with round cells and by the development of fibroblasts and collagen fibrils. The endothelial cells also proliferate and the total result is a gradual obliteration of the capillary channels and the transformation of the tuft into a solid tissue. This becomes increasingly more sclerotic and in the end may be represented by a mass of hyaline collagen in which a few atrophied cells and leucocytes remain. (Plate XCVI.)

In the extracapillary form the inflammatory lesions are not so definitely limited. All the processes that have been described in the intracapillary form occur in the tuft, but the capsular space becomes filled with exudate. In the acute forms of the lesion this exudate consists of fibrin, polymorphonuclear leucocytes and red blood cells. (Plate LXXXVIII.) The latter often predominate and as has been previously described, may remain discrete or be consolidated into blood casts. Proliferative changes are almost always observed even from the beginning and in this sense the lesion is generally subacute rather than acute. The exudate in the capsule is organized by the ingrowth of fibroblasts from the tuft and from the denuded parietal wall of the capsular space. Endothelial cells also invade it and probably among these are included the thin epithelial cells which line Bowman's capsule. In this manner the exudate is transformed into a tissue, and this when properly cut by the section is the crescent described by earlier writers. (Plate XC.)

The outcome of this type of glomerulitis is similar to that just described. The tuft is fibrosed and contracted, and the capsular space is obliterated by connective tissue either completely, or adhesions form between the shrunken tuft and the parietal wall of the capsule leaving irregular spaces still open. (Plate XCII, XCVI.)

Both these lesions are found in every case of hemorrhagic Bright's disease, in the great majority of cases more or less irregularly mixed throughout the cortex. In a few of our cases, the intracapillary type predominated, but there is apparently no reason to distinguish between types of kidney disease on the basis of this lesion.

Our study has added nothing to our scant knowledge of the etiology of these lesions. No particular attempt was made along these lines it must be confessed, for repeated investigations by others have shown that the bacteria, in particular streptococci which are from clinical evidence suspected of responsibility, are certainly not present in demonstrable form in the glomeruli, so that it seems reasonable to suppose that the damage is the result of some toxic substance. Experimental study has also not been of much aid in elucidation of the problem. It is a simple matter to damage the glomeruli of animals with chemical or even bacterial products and even streptococci and their toxins have been used in this way. The damage to the glomeruli, however, which resembles to a certain degree that occurring in human nephritis, heals with scarring. Here too there is a superficial resemblance to the end results of a glomerulitis, but the experimentally produced lesions lack the continued progressive activity which is so characteristic of the human disease. Even repeated injections of the irritating materials into the circulation of the animals fail to produce this essential phenomenon.

We have no very certain knowledge as to the effect that these processes may have on the function of the glomeruli. When completely fibrosed so that their vascular channels are obliterated we can of course be sure that their function is lost. In the earlier stages of the process, however, there are definite evidences of an increased permeability in the glomerular membrane. Most of the protein found in the urine is derived from the blood stream and as we have seen the membrane may be so grossly damaged as to allow the escape of red blood cells. Filtration of substances would therefore be increased by these lesions, provided the blood supply had not been lessened by the inflammatory process. But this process may either increase the blood supply to the tuft as a result of hyperemia or decrease it by means of capillary thrombosis. The function of the glomerulus would therefore be the resultant of these two factors, blood supply and permeability.

That this theorizing is not purely speculative is supported by experimental procedures with the simple kidneys of the frog. With them and by the method of perfusion where the amount and nature of the circulating fluid can be accurately controlled, it was possible to obtain from damaged glomeruli either increased or decreased filtration of both water and solids by modifying the two factors of permeability and supply of fluid.[47]

In all this we have spoken only of filtration, a process which may reasonably be supposed to occur in the glomerulus. If the glomerulus also secretes by means of some "vital" function of its endothelium, a possibility for which there is some direct evidence, the problem is enormously complicated. In short, little if any conclusion can be drawn from morphological examination in the present state of our knowledge as to the function of the glomeruli of a kidney suffering from hemorrhagic Bright's disease.

Contrasting with these glomerular lesions which we have just described are those of a different type. These are the focal necrosis, and their healed effects, described by Löhlein[48] and Baehr,[49] that are the result of embolic obstruction of capillary loops in the tuft by clumps of bacteria which are derived from an associated bacterial endocarditis. We shall discuss at a later time the relation of a "nephritis" due to such lesions to other forms of Bright's disease and wish here only to emphasize certain points. In the first place, toxic substances may produce by means of capillary thrombosis lesions in the glomerular tufts which, save for the presence of bacteria, are essentially similar in their appearance. Plate XCI shows such an example, for in this case a complete autopsy showed no possible source of emboli. Secondly, in bacterial endocarditis, as in any septic infection, the blood stream is flooded with toxic products. It is not surprising therefore that

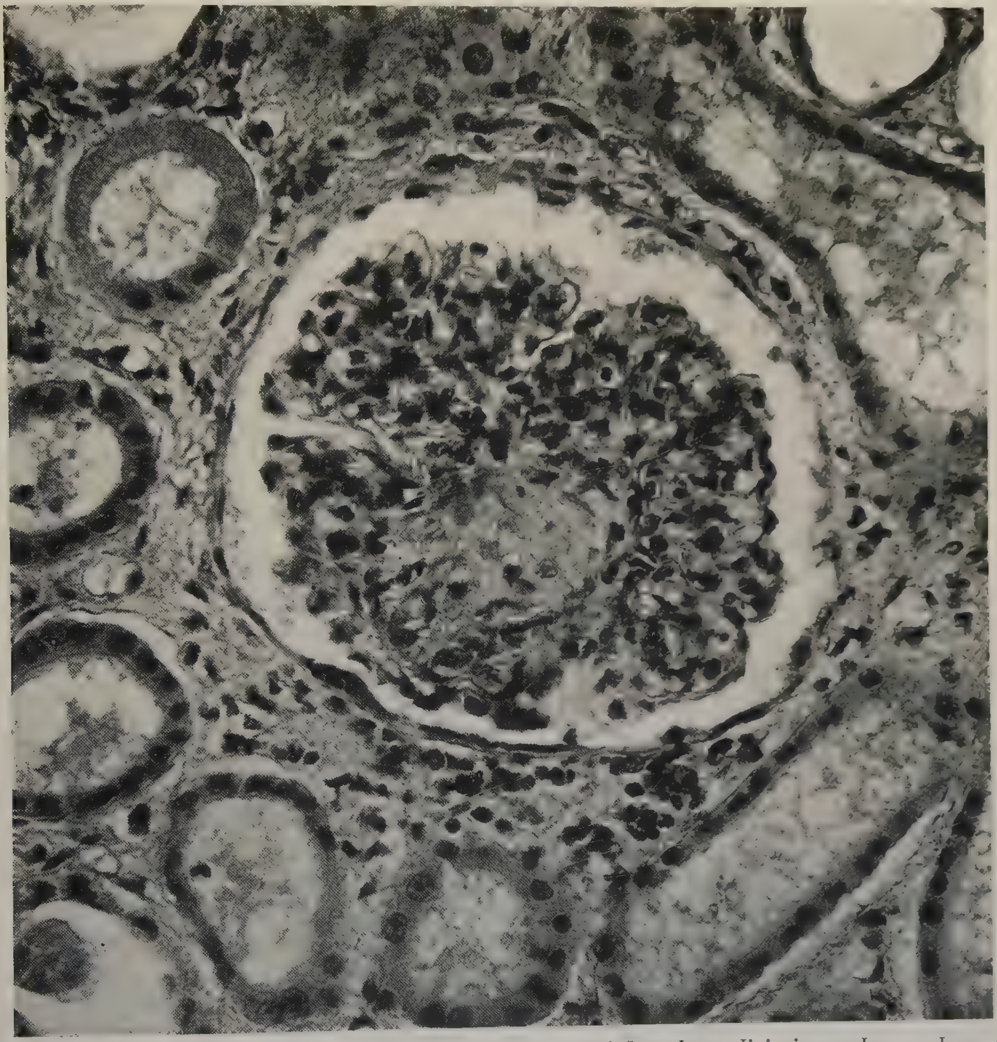

FIG. 18. A focal embolic lesion from a case of bacterial endocarditis in a glomerulus of a kidney which showed a typical "diffuse glomerulonephritis." (Cf. Plate XIII A and B.)

"diffuse glomerulonephritis," the typical result of such a condition, is frequently found and because of these facts "mixed cases" (Volhard and Fahr) also occur in which beside focal embolic bacterial necrosis of the loops (Fig. 18), in other tufts intraglomerulitis or extraglomerulitis is found diffusely distributed through the kidney cortex as a result of toxic damage (Plate XIII A). We shall describe two such cases (Cases VIII and XIII) and discuss their significance at a later time.

ARTERIOSCLEROSIS AND ENDARTERITIS

The arteries and arterioles of the kidney in all forms of chronic Bright's disease present changes which for the present we may designate with the non-committal term of scleroses. As the details of these processes have been repeatedly studied the controversy as to facts has become notably less, but when the relation that these lesions may bear to other lesions in the kidney and the interpretation of their significance in the development of the various forms of Bright's disease is considered, considerable uncertainty and disagreement are found.

The observed facts may be briefly stated, for the reader is doubtless familiar with them. In all chronic forms of Bright's disease, though to a lesser degree in the degenerative types, proliferative sclerotic processes are found in the larger arteries of the organ which as the intensity of the kidney lesion increases, include in their involvement even the smallest arterioles. In the larger arteries it is the intima which most markedly suffers. An irregular fibrous thickening of this layer develops, to such an extent that in the end the lumen of the vessel may be considerably encroached upon. In this fibrous tissue are found a few scattered fibroblasts, but cells of any sort are often remarkably absent from the diffuse masses and layers of hyaline collagen. The endothelial cells, particularly in the medium and smaller sized interlobular arteries, on the other hand may show a considerable proliferation with a consequent reduction of the lumen.

The lesions just described are constantly found in sclerotic arteries. Jores[50] has described another type of proliferative change which is found not infrequently and which he designates "hyperplastic intimal thickening" to distinguish it from the "regenerative type" of lesion we have described above. It consists of a development of elastic fibrils laid down in concentric layers in the thickened intima. (Plates LXV B and LXXX.) Now it seems to have become widely concluded that Jores in discussing these two histological pictures wished to establish them as two different diseases of the arteries, and since he was discussing "arteriosclerosis" and "endarteritis" it is apparently believed by some that he identified "arteriosclerosis" with the hyperplastic elastic tissue intimal thickening and made it the criterion and *sine qua non* of this disease. As a matter of fact, he states quite clearly: "Ich erachte daher die Form der hyperplastischen Intimaverdickung als einen für die Arteriosklerose unumgänglichen Bestandteil.

Damit is nun allerdings nicht gesagt, dass bei der genannten Gefässerkrankung die hyperplastische Intimaverdickung rein vorkäme. Das ist sogar am häufigsten nicht der Fall. Es zeigen sich Modifikationen der erwähnten Form der Intimaverdickung und Kombinationen mit dem zweiten Typus, dem der regenerativen Bindegewebswucherung der Intima" (p. 56). And, "Die Arteriosklerose der kleinen Arterien zeigt im Aufbau der Intima *beide* der aufgestellten Formen" (p. 59, italics ours). In other words regenerative connective tissue proliferation and hyperplastic elastic tissue formation are two forms of *intimal thickening*, not of arterial disease, and the experienced would hesitate to go through a section of diseased tissue sorting out by any such means those arteries which are suffering from a "pure arteriosclerosis" from those whose affection is an "endarteritis." Such sharp distinctions might be of the greatest value in the estimation of the significance of the arterial lesion in its relation to chronic Bright's disease if they could be accurately drawn, but as we shall see, later work has shown that we cannot depend on such a simple means of differentiating the complex conditions that exist in chronic Bright's disease.

It is in the interpretation of these findings and in particular in the correlation of them with the genesis and development of chronic kidney disease that opinion varies so markedly. We cannot review the literature of the subject, nor is such a review needed as extensive consideration of it may be found in the works of Jores, Fahr, Ophüls,[51] Fishberg[52] and others, but since we must take some stand in the matter even if it be a precarious one in order to proceed with our consideration of the subject, what follows is to be regarded not as in any sense generally accepted opinion or as dogmatic statement, but only as a hypothetical basis for our immediate purpose.

We believe certain points may be accepted as determined. First, that a sclerotic arterial lesion is responsible for that form of Bright's disease which was long considered a "chronic interstitial nephritis" and which is now generally designated as "arteriosclerotic nephritis." Secondly, that though sclerosis of the kidney arteries is extreme in this form of Bright's disease a similar lesion is also found, and often to a similar degree, in those secondarily contracted kidneys which are the end result of a chronic glomerulonephritis. Baehr and Ritter[53] have recently summarized and confirmed our knowledge on this point, employing not only the histological method in their morphological study but also the method of vascular injection. They found in all of their cases of chronic glomerulonephritis arterial disease "as widespread and as significant as in the primary contracted kidney" (arteriosclerotic nephritis).

The results of our histological study correspond entirely to this statement. We could see no subtle yet characteristic differences between the thickening of the intima and other evidences of vascular sclerosis in the large and middle sized arteries of our cases of arteriosclerotic Bright's disease and those of the cases of terminal hemorrhagic Bright's disease. The arterioles in the later type of the disease were indeed often not so intensively involved as in arteriosclerotic Bright's disease, nor did changes occur in the glomeruli so obviously and frequently as a result of arteriolar thickening.

The nature of these sclerosing lesions in the arterial wall has been differently interpreted by different investigators, and since the question is that which has arisen in the study of general arteriosclerosis and is equally involved in hypothesis and controversy, the reader will understand our brief discussion of the matter. The idea of Virchow that the process was an example of an inflammatory reaction has in recent times lost many of its supporters. Ophüls has pointed out however a certain value in this conception at least in a modified form, and has shown how well such an interpretation fits in with not only the histological changes in the vessels themselves, but also with what is known of the etiological factor of chronic sepsis as a cause of both arterial sclerosis and chronic Bright's disease.

The majority of recent writers however emphasize the importance of mechanical factors as a cause of not only general arterial disease, but also those lesions which develop in the arteries of the kidney in chronic Bright's disease. Degenerative and hyperplastic changes, a response to this factor, are considered to be of varying importance in the development of the disease by different observers. According to Fahr, Fishberg, and Baehr and Ritter the mechanical factor in chronic diffuse glomerulonephritis is the result of the obliteration of the capillaries of the glomeruli. This obstruction to the peripheral blood flow in the end capillaries is presumed to throw a greater "strain" on the arteries of the organ, and Hayman[54] has indeed recently demonstrated by the method of perfusion that an increased resistance to the passage of fluid through the vessels is particularly marked in such forms of nephritis whereas it is absent in kidneys showing only degenerative lesions.

Sclerosis of Glomeruli

Under this term we describe the process which destroys the glomeruli in those cases of Bright's disease which are the result of renal arteria. sclerosis.

Although the lesion takes on the form of a fibrosis and in the end results in a hyaline obliteration of the tuft which may resemble in its appearance the end stage of the chronic inflammatory processes of a glomerulitis in terminal hemorrhagic Bright's disease, most authors are agreed that the nature of the lesion is essentially different.

The obliteration of the tuft and capsule may come about in two ways. When the sclerosing process already described has extended down into the finer arterioles of the cortex it reaches at last the afferent vessel of the tuft. In these small arterioles, whose walls consist of endothelium, collagen fibrils and a few muscle-like cells, the lesion is comparatively simple and consists of a proliferation of the collagen fibrils and a consequent production of hyaline thickenings. The extension of these processes may be followed into the tuft of the glomerulus, at first in a few tortuous capillaries and then spreading until all of the capillary loops are involved. Thrombosis may occur with necrosis of a part of the tuft as well as a diffuse widespread atrophy of the tissue cells. Associated with and accompanying this capillary obliteration goes a proliferation of the connective tissue, so that as the capillaries decrease the interstitial tissue between them increases and the end result is a nodule of hyaline collagen in which a few atrophied degenerating cells, the remnants of the tuft tissue, remain. (Plates LXXXI, LXXXII, LXXXIII.)

Such is the more common method of glomerular destruction which is found as a result of arteriolar disease. Another method of obliteration is observed when the glomerulus as a whole is enclosed in a scar which has developed in the cortical tissue as a result of this same vascular obliteration. The circulation in such a tuft is sooner or later impaired and it therefore collapses and atrophies. In the meantime the proliferation of connective tissue about the capsule isolates and compresses the glomerulus, the capsular space is reduced and in the end the entire structure takes on a similar appearance to the result just described. The cystic dilatation of the glomerular capsule so commonly seen in arteriosclerotic Bright's disease has been previously discussed.

These processes, as we have described them, are those of degeneration and atrophy. The prevalence of accompanying inflammatory lesions is a matter of some dispute, or rather the significance and importance of the fairly commonly encountered inflammatory lesions is differently interpreted. Such lesions are usually minor in degree and extent and all are agreed that even when present, are of a different character from those acute exudative processes found in hemorrhagic Bright's disease in which there is an active glomerulitis. These inflammatory lesions are however of sufficient importance to have given rise to the special "combination forms" in which arteriosclerotic and inflammatory lesions both prevail but we shall give our interpretation of their significance in our later discussion of classification.

Similar processes of fibrosis occur throughout the interstitial tissue of the cortex in arteriosclerotic Bright's disease, and as a result very considerable portions of the kidney parenchyma may be destroyed and replaced by dense hyaline scar tissue. As is the case of the similar lesions in the glomeruli, the commonly accepted interpretation of the nature of these changes is that they are an atrophy of the nobler elements of the tissue, a result of nutritional disturbance, with replacement fibrosis. Analogies have been drawn between these changes and the development of those scars in the myocardium that accompany coronary sclerosis. It must be noted again, however, that in both these instances attention has been repeatedly called to the occurrence of definite inflammatory lesions in the areas of fibrosis. In the scars in the kidney in particular, round cell infiltration is frequently found, so that some prefer to look upon the changes as a result in part at least of a true inflammation rather than as a simple atrophy with connective tissue replacement. This inflammatory process is presumed to originate in the arteries where it is the cause of sclerosis and to extend down into and involve the tissues in much the same way as rheumatic and syphilitic inflammations spread. But these are matters which we may discuss more properly under the subject of classification and the reader will there find them considered.

There is little disagreement concerning the lesions themselves. Concomitant atrophy of the tubules and connective tissue proliferation go hand in hand until large areas of the cortex are destroyed. The atrophy of the tubules is doubtless the result of several mechanisms. Direct pressure atrophy from the contracting collagen may occur, nutritional atrophy from the obliteration of the intertubular capillaries doubtless is a factor, and the destruction of the glomerulus as already described may also introduce the factor of an inactivity atrophy, since the tubule is so closely dependent on glomerular activity for its proper function.

The appearances in these atrophied tubules and in those which have combined dilatation and atrophy as a result of terminal obliteration have already been described. The destroyed structures lie in dense connective tissue which contains many fibroblasts in the early stages of its development but which ultimately is transformed into hyaline collagen. (Plate LXXXIII.) At times, as already noted, there may be a very considerable infiltration of the scar tissue with inflammatory leucocytes, both lymphocytes and plasma cells. When the masses of connective tissue reach the surface adhesions to the capsule are formed and as the collagen shrinks retracted scars are produced which in the end may be sufficient in extent to produce a "contracted kidney."

Associated with these scars are found the sclerotic arteries, apparently bearing the same relation to the mass of scar tissue as a thrombosed artery does to a renal infarct. From this similarity in part, comes the widely accepted interpretation of the process as an "anemic atrophy" (Fahr). The occurrence of occasional small areas of frank necrosis in the glomeruli and other tissues supports this conception, and the presence of some inflammatory reaction in the lesions, as we shall emphasize later, need not cause us to discard entirely this interpretation.

CONGESTION OF THE KIDNEY

The part played by vascular congestion in the development and course of Bright's disease has been particularly well emphasized by Oertel. Since a chronic venous congestion may of itself alone produce not only marked functional but also definite anatomical changes in the kidney, it is not surprising that its effects are noted to an exaggerated degree in an organ which is already disturbed by severe lesions. Congestion of two sorts occurs.

The simplest case is the diffuse congestion of the kidney in Bright's disease which is the result of failure of the general circulation during the terminal phases of the disease. Such examples are particularly well illustrated in arteriosclerotic Bright's disease where the load of the failing circulation is thrown upon the already damaged kidney. The occurrence of this event is especially obvious and easily recognized clinically, because the urinary changes are relatively slight until this complicating factor occurs. It will be noted in the clinical descriptions that not infrequently the characteristics of the urinary findings changed in the terminal period of the disease. An increase in albuminuria, evidences of epithelial degeneration and even bleeding often confused the clinical picture to such an extent that it was difficult to distinguish the condition, if seen then for the first time, from terminal hemorrhagic Bright's disease. In such kidneys the vessels, and in particular the veins and capillaries both in the cortex and medulla, showed a marked engorgement with blood. The glomerular tuft was distended and its capillaries crowded with red blood cells. The effects of these changes could be seen in the degenerating tubular epithelium and in the presence of albuminous fluid in the capsular space of the glomeruli.

Experimentally it is easily demonstrated that passive congestion of the kidney may produce these acute changes in the tubules and glomeruli. Whether long-continued congestion may produce extensive proliferative changes in the interstitial tissue of the kidney is not so easily answered. Oertel describes "contracted kidneys" as a result of chronic passive congestion of the organ. We have found no such extreme changes either in the present series or in our general experience with diseases of the kidney.

The other type of congestion found in Bright's disease is the local congestion of some of its vessels which results from the partial obliteration of its vascular bed. Such changes are particularly pronounced in the late stages of a terminal hemorrhagic Bright's disease. The vascular system in such an organ may be profoundly altered by the obliteration of glomeruli and the compression of veins by scar tissue, as well as by the occlusion of arterioles by sclerotic processes. As a result, throughout the cortex are seen large irregularly dilated channels, or areas where the capillaries between the tubules and in the scars are greatly distended and packed with red blood cells. (Plate XCVII.) The capillaries of the medulla and vasa recta are often so tremendously distended that the unexperienced may mistake them for tubules filled with blood and associated with these congestive phenomena are degenerative processes in the epithelium. Although it may be entirely impossible in such a kidney to pick out either the functional or anatomical changes which are the direct result of this irregular congestion and to distinguish them from the other degenerative lesions which are caused by the primary noxus of the disease, from what we know of the results of uncomplicated congestion of the kidney there seems to be no reason to doubt that they are playing an important part in the development of both the functional and anatomical processes which characterize the late phases of Bright's disease.

We have emphasized the importance of congestion in Bright's disease because it is doubtless one of the chief factors which obscure the clinical diagnosis in the later stages of the disease. Baehr and Ritter, have pointed out the difficulties of distinguishing by clinical means what exact type of "contracted kidney" is present, and believe that this arises from the fact that the arteries in both arteriosclerotic Bright's disease and "diffuse glomerulo-nephritis" are similarly affected. As we have already stated there is no question that this is so, but we are inclined to think that the congestive factor is equally if not more important in producing the confusing clinical picture than is the sclerosis of the arteries.

METALLAXIS

This term, which one does not find in general usage as frequently as we believe its value warrants, was originated by Jores[55] to designate the transformation or building-over of an organ by pathological processes. In such chronic diseases as cirrhosis of the liver and Bright's disease there occurs a tearing down of the structural units of the organ involved, reparative processes in these elements and a final building up of them in an irregular fashion along with connective tissue proliferation. These changes, intermittently repeated over the course of years, result in a more or less complete reconstruction (*Umbau*) of the organ, so that it no longer differs in a simple quantitative way from its original structure, but is in fact a new organ, not designed on its original plan but with a completely altered architecture. A kidney in the last phases of a terminal hemorrhagic Bright's disease is therefore not a kidney plus or minus certain morphological characteristics, but an organ which in the stricter sense is no longer a kidney.

This fact, of greatest importance to the clinician and pathologist who are attempting to correlate the results of their respective studies to a proper understanding of the disease, has not received perhaps the attention which its importance deserves. Oertel has discussed this matter and pointed out some of the remarkable changes that have occurred when the disease has reached the terminal stage of a contracted kidney.

As we have previously stated the distribution of the inflammatory lesions and the resulting destruction of the kidney parenchyma may be of either a diffuse or patchy nature. For this reason two types of alteration of the kidney architecture are found which may be designated as a diffuse or a patchy metallaxis. The histological pictures of such kidneys differ strikingly. Plate XI A illustrates the diffuse and Plate XXIV A the patchy type, but the functional effects seem to be essentially similar. In either case when sufficient functioning tissue is destroyed the kidney fails and uremia develops. Let us consider then the general structure of such a kidney, summarizing briefly the changes which we have already detailed under separate headings.

Such a kidney has few if any glomeruli. Its tubules have disappeared throughout large areas of the cortex, either by actual destruction of their tissues or by occlusion. Those which remain are lined with an epithelium which morphologically resembles only remotely the original tubular epithe lium and, judging from experimental work, which probably differs equally from the normal in its functioning ability. The degenerative changes, such as cloudy swelling in other tubule cells, for all we know may have increased or decreased their vital activity. Progressive changes, such as hyperplasia and hypertrophy, have altered the size and course of the tubules, and the functional significance of these changes is entirely obscure, for it is pure assumption that their increased size or number corresponds to any increased ability in function.

The vascular system has been completely rebuilt by the development of connective tissue both in the interstitial framework of the kidney, in the glomeruli and in the arteries. As a result less blood is available through the arterial supply, and the obliteration of veins has interferred with proper drainage of the organ and produced the complicating factor of congestion. *The blood no longer first passes through the glomeruli, which has been in great part occluded, but passes directly by Ludwig's vessel to the tubules.* This is a point of the greatest importance, for judging from recently acquired knowledge of the part the glomerulus plays in the removal of substances from the blood before it reaches the tubules, it is quite likely that the function of the latter under these circumstances is a response to entirely different conditions than are found when the normal tubule functions. The membrana propria of the tubule has been greatly thickened, which most certainly must modify processes of diffusion or secretion which normally occur in one direction or the other through it between the blood stream and the urine in the lumen of the tubule. And often many if not most of the intertubular cortical capillaries have been obliterated by connective tissue formation, so that the blood is shunted directly to the vasa recta of the medulla. What the straight tubules in this region may do with this blood which has not been through the usual processes of renal activity we have no knowledge.

This is a brief if incomplete statement of conditions as they exist in chronic Bright's disease, but it is sufficient to illustrate the point which we wish to emphasize. And that is, that were we entirely familiar and certain of the function of all the elements of the normal kidney and of the relations of these various processes one to the other we should still be far from an understanding of the function of the "kidney" of chronic Bright's disease. For here we have a kidney only in the convenient sense that it once possessed the elements and architecture of that organ. The mysteries of its functioning cannot therefore be deduced directly from any physiological experience and the pathologist and clinician must determine for themselves the altered activities of this newly created mechanism of strange and unusual design. But these are matters for a later consideration.

CHAPTER VII

THE CLINICAL AND PATHOLOGICAL OBSERVATIONS*

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* T. A. and J. O.

Hemorrhagic Bright's Disease

THE ACTIVE STAGE

CASE 1

Kelly B. Aged twenty-four.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Six months (?). Observed during the last week.

Etiology. Scarlatinal streptococcus?

Course. There was a generalized red skin rash in September 1927 for which he did not consult a doctor. On February 14, 1928, while feeling perfectly well, he observed a slight edema of his feet. By March 1, 1928, he had a general anasarca and albuminuria and hypertension were found. On March 5 there was blurring of vision. On March 7 he was admitted to the hospital. The urine showed evidences of an intense inflammatory process. The blood urea was 189 mg. per 100 c.c. and rose rapidly during the next few days. He died of uremia on March 14, 1928.

RELEVANT CLINICAL DETAILS

In 1922 and again in 1926, two years before his death, he had his blood pressure and urine examined and he was passed as normal.

There had been no illnesses of any moment since 1926 except that in September 1927 he found that he had a generalized rash over his skin. He was anxious not to stop work and since he was not noticeably ill he did not consult a physician.

On February 14, 1928, while feeling perfectly well he had some difficulty in putting on his shoes and observed then a pitting edema of the ankles and feet. He did not consult a doctor about this edema until February 23 when it was found that he had protein in his urine. He nevertheless continued at work and on February 26 played five sets of tennis. Towards the end he was bothered a good deal by muscle cramps. He felt nauseated next day and did not go to work, but feeling better on February 28 he went to the office. On March 1, however, he had a marked swelling of the face and called in a doctor who insisted on his going to bed. On March 2 he had a severe headache, felt nauseated and was conscious of a pain in the small of his back. On March 5 his vision became blurred.

He was admitted to the hospital on March 6. There was a general anasarca involving the whole skin, with marked soft edema of the arms and legs. There was fluid in both pleural cavities and a moderate ascites. There was no cardiac enlargement. The blood pressure was 180 systolic and 105 diastolic. The arteries were not thickened. There was intense retinal edema which obscured large areas so that the vessels could scarcely be seen. There was only one small hemorrhage in one eye.

A twelve hours' urine had a volume of 143 c.c. and a specific gravity of 1.018. There were 2641 mg. of protein per twelve hours. The number of casts was 107,000 per twelve hours, all of them renal failure casts. The blood urea concentration was 189 mg. per 100 c.c. The red blood cells were 452,000,000 per twelve hours and white blood cells and epithelial cells 30,000,000. A particularly noteworthy feature of the sediment was the large number of "oval fat bodies," a term given to large cells which in this case varied between 15 and 35 microns in diameter and were full of large granules. The number per twelve hours varied from 249,000 to 4,300,000.

By March 9 the blood urea concentration had risen to 235 mg. and one kidney was decapsulated that evening. The urine volume however continued to decrease and the patient died on March 13 of pulmonary edema. The twelve hour rates of excretion are shown in Table XVIII:

Table XVIII

Date	Casts	R.B.C.	W. & Ep. C.	Protein	Vol.	Blood urea, mg. per 100 c.c.
				mg.	c.c.	
March 7.........	107,000	452,000,000	30,000,000	2,641	143	189
March 8.........	86,000	413,000,000	35,000,000	2,286	124	
March 9.........	95,000	285,000,000	4,200,000	1,707	79	235
March 10.........	0	27,400,000	1,400,000	.....	66	257
March 11.........	114,000	126,000,000	12,000,000	704	48	293
March 13.........	37,000	1,370,000	1,600,000	.....	28	

From the general clinical standpoint this, of course, was a "terminal" condition, yet from the narrower point of view of the renal lesion alone, the condition was "active" in the sense that we had evidence in the urine of an intense inflammatory and degenerative process, and it was therefore classified as a hemorrhagic case in the active stage.

PATHOLOGICAL OBSERVATIONS

The kidneys alone were obtained after death. They were somewhat swollen, measuring 14 × 7 × 5 cm. Their external surfaces were smooth, a dull purplish red in color and definite petechial hemorrhages could be seen. The cut surface showed the same congestion and some thickening of the cortex. The medulla and pelvis were normal. The renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus examined is the seat of a violently active glomerulitis. The tufts are increased in size and heavily infiltrated with mononuclear and polymorphonuclear leucocytes. Some of the capillaries are collapsed while others are filled with fibrin thrombi which contain polymorphonuclear leucocytes. Occasionally areas of necrosis with nuclear debris are seen scattered through the substance of the tuft. The capsular spaces contain leucocytes and fibrin, and occasionally red blood cells. In others definite organized glomerular crescents are present. There is a development of some connective tissue both in the tufts and as adhesions in the capsular space.

Tubules. Scattered among the convoluted tubules of the cortex are groups of cross sections of the tubules which show a marked cloudy swelling with the accumulation of large granules in the tubule cells. The majority of the tubules have a more normal epithelium, however, though there is a considerable desquamation of cells in many of the tubules. Others show definite evidence of regeneration, the tubule cells being large and irregular in shape. Where interstitial connective tissue proliferation has occurred the tubules are collapsed and their epithelium atrophied. In the cortex most of the convoluted tubules contain casts of all sorts, and also red blood corpuscles and desquamated cells. In the medulla are many renal failure casts.

Interstitial Tissue. Throughout the entire cortex there is a diffuse cellular proliferation of the interstitial connective tissue. This new tissue separates the tubules to an abnormal degree and is heavily infiltrated with mononuclear and polymorphonuclear leucocytes. Similar lesions, but to a much less marked degree, are seen in the medulla.

Arteries. The arteries including the arcuate and interlobular branches are essentially normal.

SUMMARY

The kidney shows an active inflammation of its glomeruli and interstitial tissue with some proliferative changes in the latter. The epithelium is moderately affected by degenerative processes. The arteries are essentially normal.

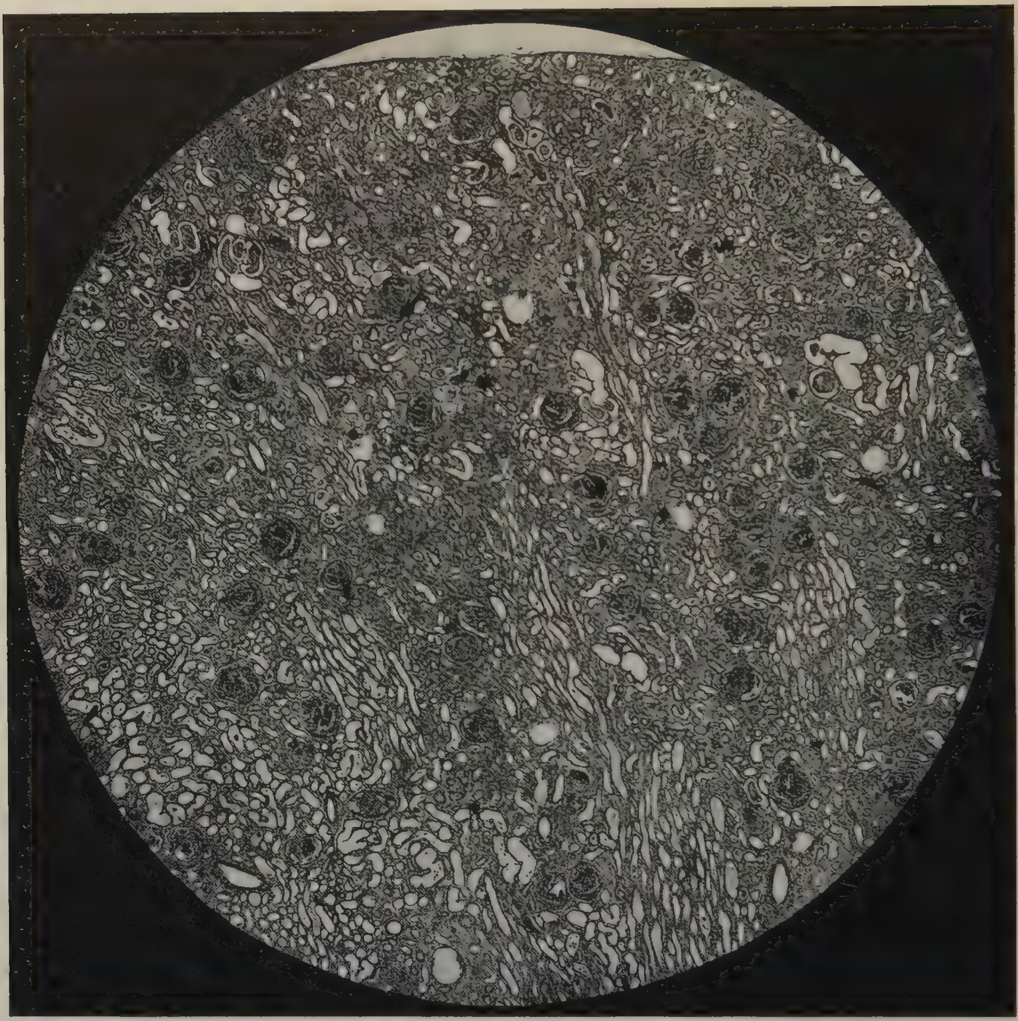

Plate I* a

The enlargement of the glomeruli, a result of an acute extracapillary glomerulitis, is evident. There is a moderate proliferation of the interstitial tissue with a consequent derangement of the architecture of the cortex. Many tubules are collapsed; others are dilated and filled with colloid material.

* For the sake of convenience plate number and the number of the corresponding case is identical throughout. For purposes of comparison Plate xlvii a may be used, as at this magnification its appearance is that of a normal kidney.

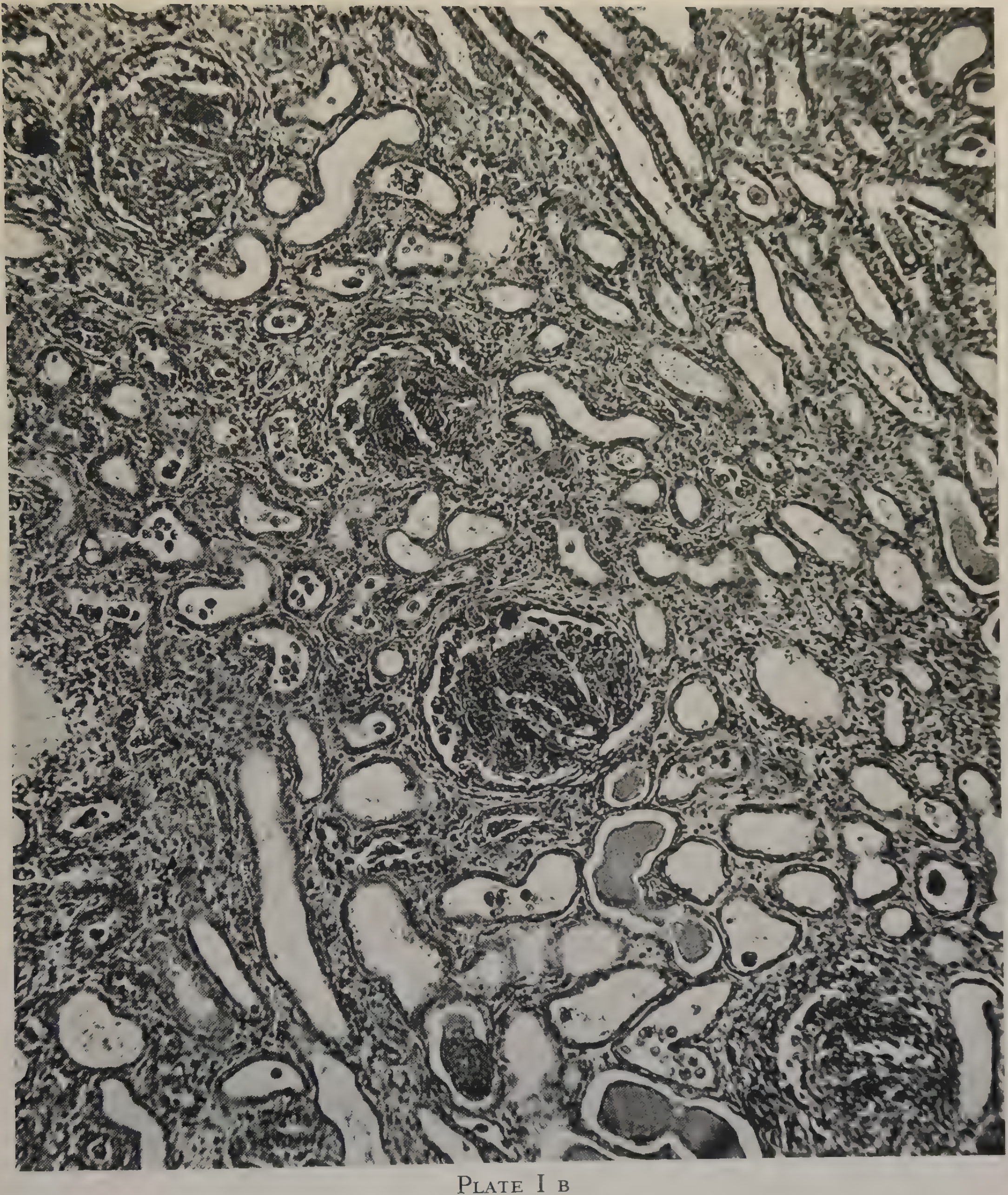

Plate I b

The inflammatory processes whose products fill Bowman's space of the glomeruli are well seen, as is inflammatory infiltration and proliferation in the interstitial tissue. The epithelium of the compressed tubules is atrophic. Their lumen contains casts or desquamated cells.

CASE II

Robert B. Aged fifteen.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. One and a half years. Observed during the last sixty-five days.

Etiology. No information.

Course. The only indication of the initial stage was the brown or red color of the urine which was seen by the boy's mother in May 1925. The urine was normal in appearance ten days later but repeated examinations of the urine made at intervals during the next year and a half always showed a definite proteinuria. On September 6, 1926, a return of hematuria was noted. On September 16 the urinary sediment showed the evidences of an active stage of the disease but ten days later some renal failure casts appeared and soon afterwards obvious clinical evidences of uremia developed. The urine differed from that seen in a fully developed terminal stage in respect to the very large numbers of casts and cells, and the intensity of the albuminuria. He died in uremia on November 12, 1926.

RELEVANT CLINICAL DETAILS

In 1918 when he was seven years old he had pneumonia followed by empyema and was very ill for several months. His mother thought that his face was swollen for a time during this illness, but the doctor who attended him stated that at no time had he observed any appreciable amounts of albumin in the urine.

In 1922 his tonsils were removed because he had suffered from several attacks of tonsillitis.

In May 1925 he contracted a cold in the head and seemed indisposed but not seriously ill. His mother happened to notice however that his urine had an unusual appearance in that it was sometimes deep brown, at other times reddish in color. She took the boy to a doctor who examined the urine and told her that it contained blood and albumin. There was no edema and he did not seem ill. It seems likely that at this time there were many white blood and epithelial cells as well as red blood cells in the urine for renal tuberculosis was suspected. Ureteral catheterization showed bloody urine coming from both ureters. Guinea pig inoculation gave negative results. Within ten days the urine was again normal in appearance and in every respect the boy seemed to be entirely well.

During the next year and a half there was at no time any serious illness but there were many minor colds in the head which were sometimes associated with cough, expectoration of yellow sputum and night sweats. He never lost more than a few days from school but he was quite definitely less robust than the average boy of his age. Throughout this period the urine was examined from time to time by the doctor who had seen him in the initial stage. Albumin was invariably found to be present but always in a rather low concentration. At no time was there any macroscopic hematuria.

About the beginning of September 1926 the latent pathological process in the kidneys seems to have flared rather abruptly into a state of great activity. He had caught one of his usual colds and had a cough with some expectoration. The only thing which distinguished this infection from many others through which he had safely passed was a slight swelling of the face and a change in the color of the urine. His mother was constantly looking for the brown or red color which had ushered in his albuminuria and now for the first time in one and a half years she saw it again.

The boy was admitted to the hospital on September 8, 1926. There was no detectable edema of the legs but his mother was sure that at times his face was definitely swollen. There was evidence of cardiac enlargement and a blood pressure of 130 systolic and 75 diastolic. There was no anemia. He had by that time quite recovered from his infection and did not give the impression that he was suffering from any toxemia. The blood urea concentration was 41 mg. per 100 c.c. Specimens of urine collected for the ordinary routine examinations all contained macroscopic blood, and a very heavy cloud of albumin but the specific gravity was not low.

On September 16 the blood urea was found to have risen to 80 mg. per 100 c.c. The first concentration test was examined on that day. The twelve hour's volume was 295 c.c. with a specific gravity of 1.013. The rate of protein excretion was 4354 mg. per twelve hours. There were 1,030,000 casts and of these 4 per cent were epithelial, 2 per cent granular, 8 per cent waxy and the remainder hyaline. No renal failure casts were found. The number of red blood cells was estimated as 1,890,000,000 per twelve hours, the urine being frankly bloody. But in addition to the red blood cells there were 79,500,000 white blood cells and epithelial cells, a number so large that when considered in conjunction with the heavy albuminuria and the large number of epithelial and granular casts they clearly indicated a very active inflammatory and degenerative process at work in the kidneys.

It is noteworthy that in spite of this intensely active renal lesion there were no other clinical manifestations by which the gravity of the situation could have been guessed. On September 24 the blood urea concentration had increased to 92 mg. per 100 c.c. and a short search through the urinary sediment showed the presence of several renal failure casts. But it was not until September 26 that the first purely clinical symptom of uremia was observed. It took the form of an easy emesis accompanied by no more than transient nausea. Next day the blood urea concentration was found to be 136 mg. per 100 c.c.

The figures in Tables XIX and XX give, though only disconnectedly, indications of the progress of the renal lesion.

It will be noted that as the blood urea concentration rose the proportion of renal failure casts increased until two days before his death it seemed that all of the casts were to be classified under this heading. In this respect the urinary evidences are in conformity with those usually found in uremia. But quantitatively the results given in Table XX are unusual, for the numbers of casts and cells, and the rates of protein excretion are greater than those commonly seen in the terminal stage. It seemed legitimate to infer an unusually intense activity of inflammation and in view of the enormous numbers of white blood cells and epithelial cells a very active degeneration and desquamation of tubule epithelium.

TABLE XIX
DIFFERENTIAL CAST COUNTS AND BLOOD UREA CONCENTRATIONS

Date	Blood urea, mg. per 100 c.c.	Blood, per cent	Epithelial, per cent	Granular, per cent	Fatty, per cent	Waxy, per cent	Hyaline, per cent	Renal failure, per cent
Sept. 10......	41							
Sept. 16......	...	0	4	2	0	8	86	0
Sept. 27......	136							
Sept. 30......	...	0	3	20	0	8	60	9
Oct. 7.......	187	0	9	10	0	17	54	10
Oct. 18......	...	0	0	0	0	0	16	84
Oct. 26......	206							
Nov. 9.......	...	0	0	0	0	0	0	100
Nov. 11......	273							
Nov. 12......	Patient died							

TABLE XX
RATES OF EXCRETION OF CASTS, CELLS, AND PROTEIN PER TWELVE HOURS

Date	Casts	R.B.C.	W. & Ep. C.	Vol., c.c.	Sp. gr.	Protein, mg.
Sept. 16.............	1,030,000	1,890,000,000	80,000,000	295	1.013	4,354
Sept. 30.............	8,880,000	23,200,000	....	202	1.025	6,980
Oct. 7...............	9,820,000	129,000,000	77,000,000	257	1.025	7,910
Oct. 18..............	3,050,000	370,000,000	143,000,000	370	1.023	12,470
Nov. 9...............	3,820,000	216,000,000	....	47	1.021	634
Nov. 12..............	Patient died					

From October 1 the clinical evidences of uremic intoxication became more and more obvious up to his death on November 12. The vomiting, at first only occasional, became so frequent as to interfere with his nutrition. There was a constantly increasing sense of weakness. On October 12 he first began to complain of pains in various parts of his body which later could only be relieved by morphine. From October 20 until a few days before his death the blood pressure curve fell gradually from 154 systolic and 99 diastolic to 125 systolic and 78 diastolic. There was a slowly increasing edema of the legs. Towards the end of October an intermittent bleeding from the nose commenced. On November 5 the red blood cells, which had been 4,870,000 on October 7, had fallen to 3,040,000 per cubic millimeter. No convulsions nor even any twitching of the muscles were observed. On the day of his death the blood urea concentration was only 273 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a marked edema of the feet, legs and scrotum. The peritoneal and pleural cavities contained clear fluid. The heart was about one and a half times the normal size. The right side was dilated, while the left ventricle was both dilated and its wall thickened. The valves and coronaries were normal. The kidneys were rather large, measuring 13 × 6.5 × 4 cm. The capsule stripped easily leaving a smooth mottled surface with purplish areas scattered on a pale greyish background. No petechial hemorrhages could be seen. The cut surfaces showed the same greyish discoloration of the cortex, while the pyramids were greatly congested. The pelvis and arteries were normal. Except for an old adhesive pleurisy and perisplenitis and a general congestion of all organs, no other significant lesions were found.

MICROSCOPICAL EXAMINATION

Sections of the various organs showed nothing of importance except congestion of the venous system. The arteries in all the organs were normal.

Glomeruli. Practically every glomerulus shows a well-developed glomerulitis of the combined intracapillary and extracapillary type. The capillaries in the glomerular tuft are compressed by the development of connective tissue between them and there is an excessive number of nuclei, chiefly of fibroblasts but also of many round cells. The capsular space is filled with organized exudate, almost every glomerulus showing a well-formed crescent. In some of these the connective tissue development in the capsular space has almost completely compressed the glomerular tuft.

Tubules. The convoluted tubules in the cortex are greatly altered by the fibrosis which has occurred in the interstitial tissue. Many exist only as solid cords of compressed atypical epithelium, in others the lumen is still preserved and is lined by a layer of atropic cells. Alternating with this type of change are seen tubules whose lumen is greatly dilated. The lumen is either apparently empty or it is filled with thick hyaline casts and is lined by flattened cells. All of these cells are somewhat granular, but no areas are found where they present any fatty degeneration. The broad ascending limbs of Henle's loop show the same lesions, some being compressed while others are dilated and many contain hyaline or granular casts.

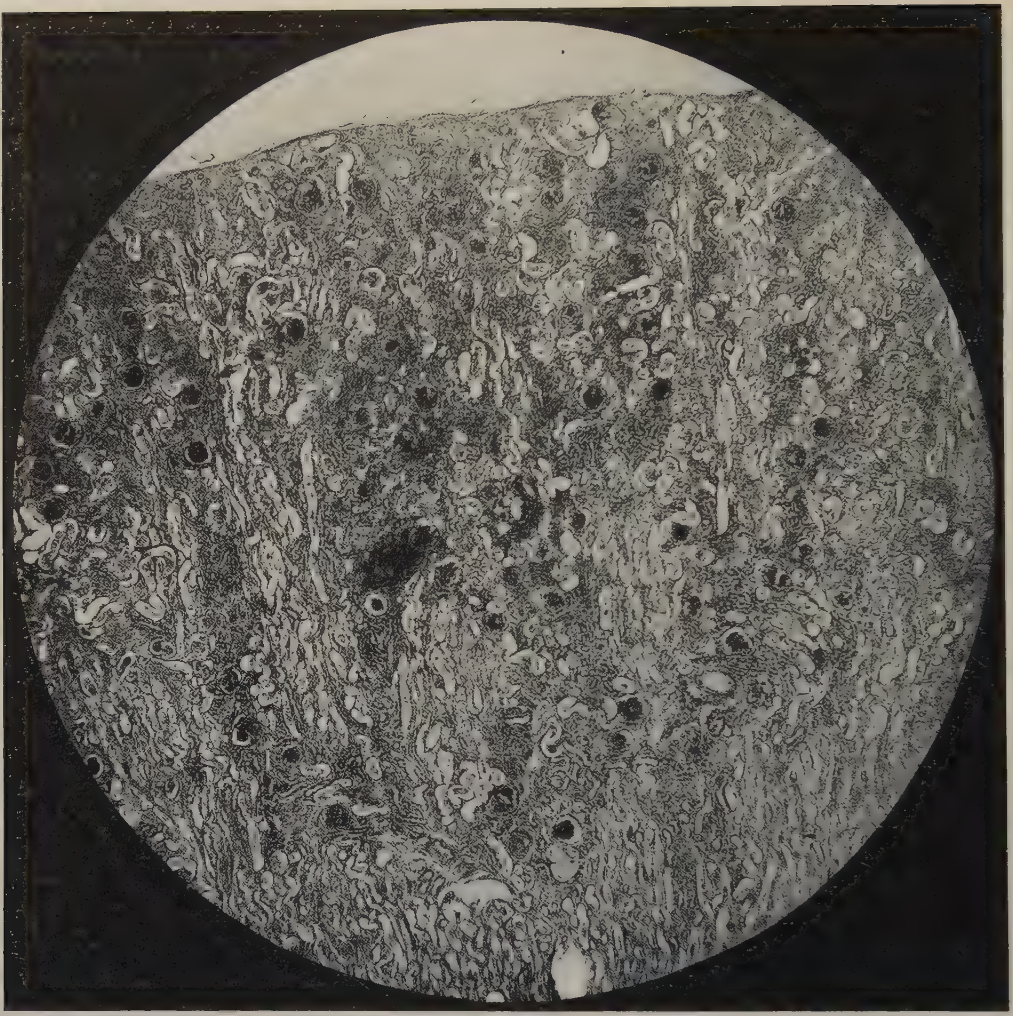

Plate II a

The glomeruli appear as small dark structures, a result of the fibrosis and inflammatory involvement of their tufts. The framework of the kidney is irregularly infiltrated with inflammatory round cells.* Many tubules are collapsed; others show a beginning dilatation.

* Round cell or leucocytic infiltration at the magnification of the low power plates does not show the individual cells but appears as an irregular dark area in the inflamed tissue.

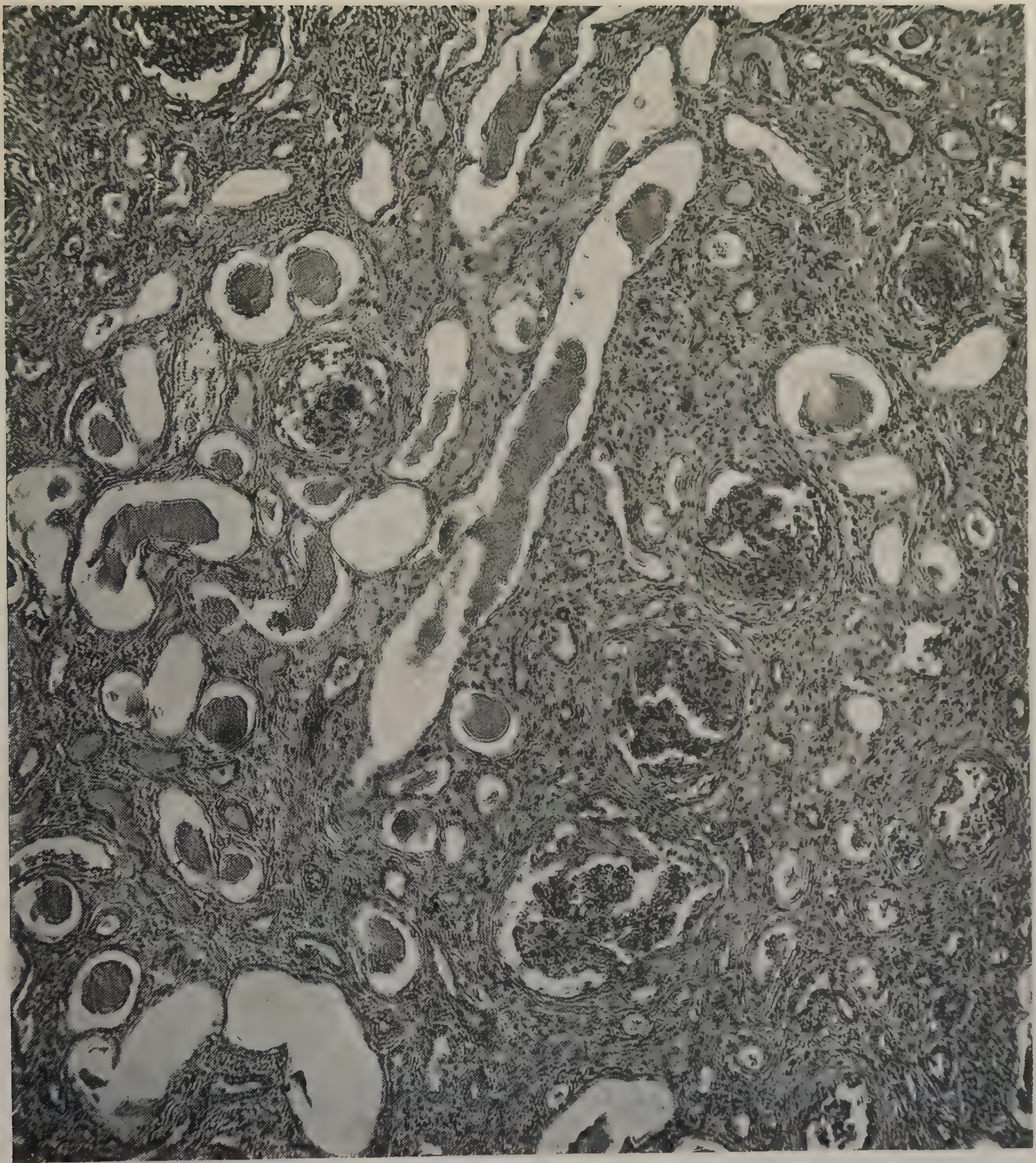

PLATE II B

There is a proliferative inflammatory involvement of the glomeruli and their tufts are reduced in size by connective tissue contraction. The interstitial tissue is greatly increased in amount and heavily infiltrated with leucocytes. The tubules are either collapsed or irregularly dilated and filled with casts.

The epithelium of the collecting tubules is better preserved and their form is not altered by the development of connective tissue about them but the majority contain casts. Many of these are broad renal failure casts, the others being hyaline and granular casts of the usual type.

Interstitial Tissue. Throughout the cortex is a diffuse development of connective tissue which is not yet entirely fibrous. The nuclei of fibroblasts are evident and in scattered places dense collections of round cells are seen. The development of this interstitial tissue is so diffuse that a considerable portion of the cortical tissue has been replaced by it. In the medulla, there is no significant increase in it.

Arteries. Both the larger arteries between the cortex and medulla as well as the smaller branches in the cortex are essentially normal. There are no significant perivascular lesions.

SUMMARY

The kidney shows a well advanced but still active glomerulitis associated with a marked proliferation of the interstitial tissue. Degenerative changes in the epithelium are slight and the arteries are normal. Renal failure casts are found in great numbers.

Case III

Marion B. Aged forty.

Clinical Diagnosis. Hemorrhagic Bright's disease active stage.

Etiology. Wound infection.

Duration. Thirty-one days.

Course. On the tenth day after a pelvic operation evidences of a septic infection appeared, and a few days later the urine was found to contain much blood and many casts. It seems probable that the infection was streptococcal in origin for shortly afterwards erysipelas developed. The blood urea concentration rose to very high levels, only renal failure casts were found in the urinary sediment, and after thirty-one days the patient died of uremia.

RELEVANT CLINICAL DETAILS

The patient had been under observation for four months on account of pregnancy and in eight routine examinations of the urine no albumin and no casts or red blood cells had been reported. It was known that the lower segment of the uterus was adherent to the laparotomy scar of a previous operation and it was thought that this circumstance would interfere with labor, so the operations of cesarian section and supravaginal hysterectomy were performed. After the operation there was severe bronchitis but at the end of a week this had cleared. On the tenth day after operation the temperature rose to 102.3°F. The abdominal wound was found to have broken open and there was a considerable amount of thin serous discharge. The fever continued and a vaginal examination on the thirteenth day after operation disclosed evidence of parametritis. The urine which hitherto had not been examined since the operation was found to contain much albumin, a large quantity of blood, and many casts. Next day the report stated that the urine contained so much albumin that it almost became solid on boiling, and the presence of many casts including blood casts was noted. It seems probable that these examinations were made at the onset of the initial stage. On the seventeenth day after operation a pelvic abscess was drained. The blood urea concentration was 128 mg. per 100 c.c. Two days after the second operation the temperature fell to subnormal levels, but the patient was very weak and the blood urea concentration had risen to 189 mg. per 100 c.c. On the twenty-seventh day after operation there was a sharp rise in temperature to 101.8°F. and a raised red margin was spreading over the face. Next day there was a chill and the temperature rose. The blood urea concentration now was 456 mg. per 100 c.c. and in the urine all the casts were of the renal failure type. The patient was now in a semi-stuporous condition. The blood pressure was low. The blood urea concentration continued to rise until it reached 594 mg. per 100 c.c. She was then in deep coma and died thirty-one days after the onset of the infection.

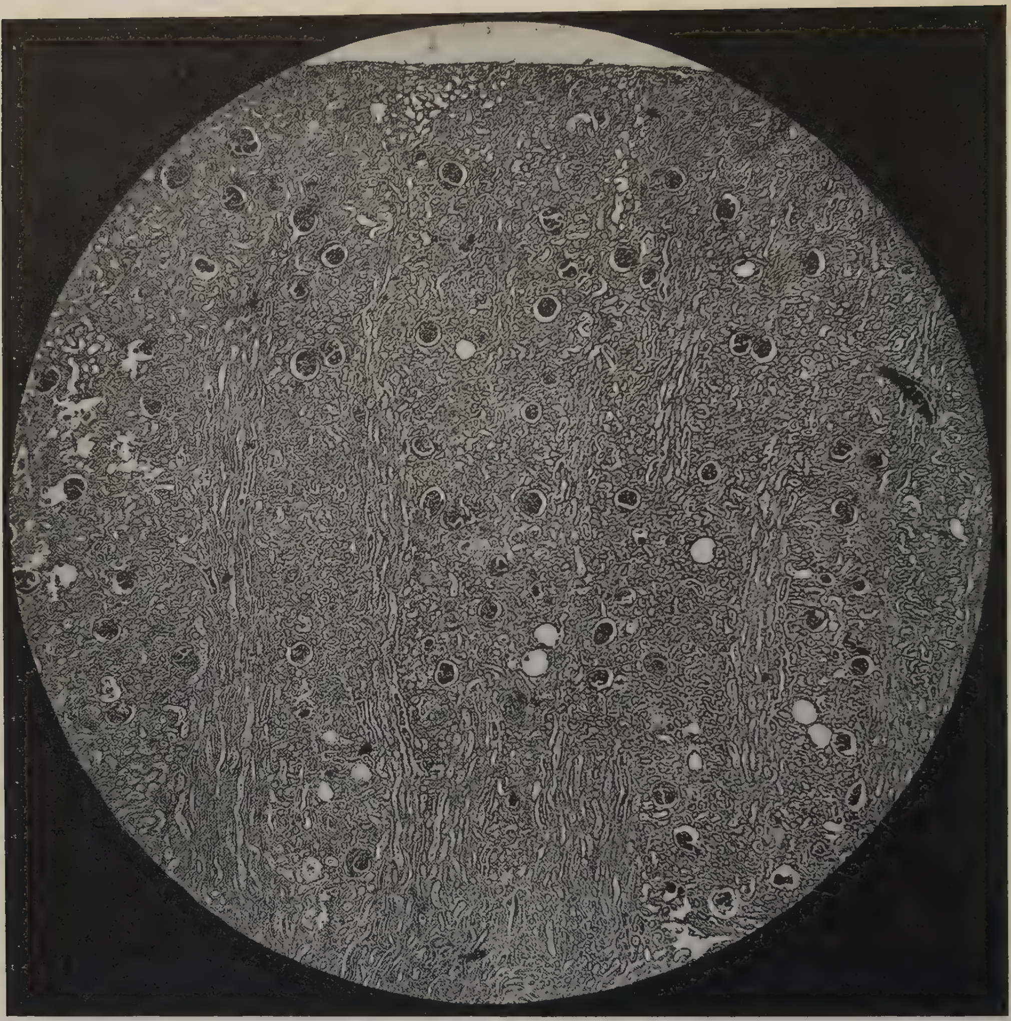

Plate III a

The general arrangement of the cortex is normal since there is only a slight proliferation of the interstitial connective tissue. The glomeruli stand out quite prominently as a result of the intracapillary inflammatory lesions in them.

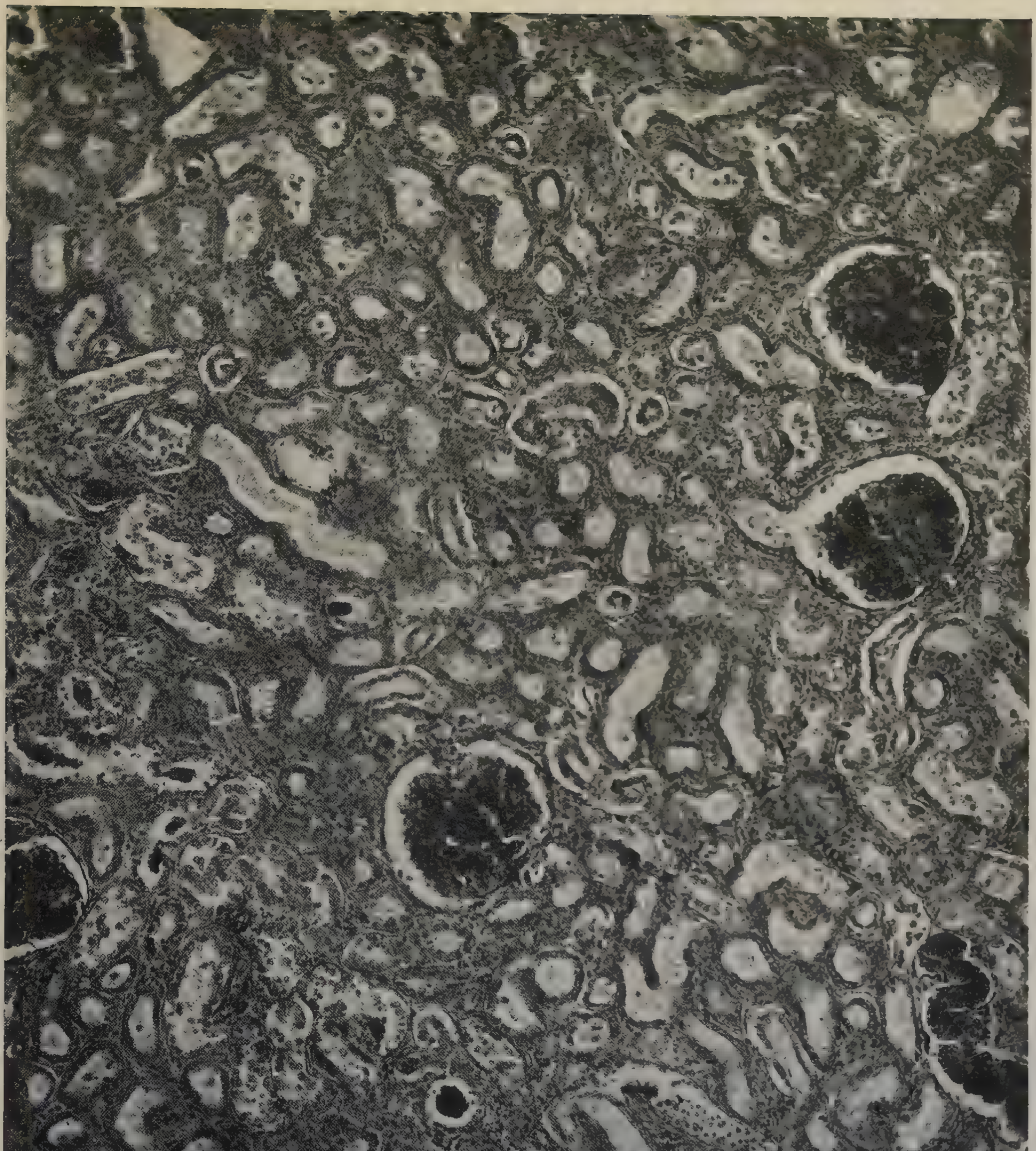

PLATE III B

The glomerular tufts are so infiltrated with inflammatory exudate that little detail in their structure can be made out. The lesions are chiefly of the intracapillary type. The structure and arrangement of the tubules is still fairly well preserved, since there is only a moderate and early stage of inflammatory proliferation in the interstitial tissue. The dark cast in the lower right section is a blood cast. (Cf. Plate XC.)

PATHOLOGICAL OBSERVATIONS

At autopsy a suppurative metritis and local pelvic peritonitis were found and a bronchopneumonia. The heart was not enlarged. Smears of the pus in the pelvis showed many gram-positive cocci. The kidneys were slightly large, measuring 12.5 × 7 × 5 cm. Their capsules stripped easily leaving a pale smooth surface on which were a few very small hemorrhages. The cut surface showed some swelling of the cortex but was otherwise normal. The renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically every glomerulus is involved. Some of them show a typical early extracapillary glomerulitis with typical glomerular "crescents," but in the majority the lesion is of the intracapillary type, consisting of swelling and leucocytic infiltration of the glomerular tuft. In none of them is there any considerable development of connective tissue.

Tubules. The general appearance of the convoluted tubules and broad ascending limbs of Henle's loop is normal. The epithelium in some of the former divisions shows a slight swelling and granular degeneration and in an occasional group of tubules the epithelium is filled with fat droplets of irregular size. In some areas the cells of the lining of the tubules are very irregular in shape and arrangement and have the appearance of a regenerated epithelium. The lumen of the tubules of the cortex contains granular material mixed with a few leucocytes, and in many are well-formed granular and hyaline casts. In the large collecting tubules are masses of granular material, desquamated epithelial cells and definitely formed large renal failure casts.

Interstitial Tissue. The only lesions in the interstitial tissue are scattered small areas of beginning connective tissue formation and slight round cell infiltration. Even in the most advanced of these there is no significant compression of the tubules as the lesion is only incipient.

Arteries. The arteries throughout are normal.

SUMMARY

The kidneys show early stages of an intracapillary and extracapillary glomerulitis. The lesions in the epithelium and interstitial tissue are slight and the arteries are normal.

CASE IV

Peter B. Aged thirty-one.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Unknown. Observed during last day.

Etiology. No information.

Course. A month before death he began to cough and felt weak. A week later there was generalized edema and a purpuric eruption. He died of bronchopneumonia twenty-four hours after admission to the hospital. The urine was smoky with blood, and the sediment contained only renal failure casts. The blood urea concentration was 363 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

The patient was without friends and was so ill on admission that no detailed history could be obtained. He had apparently considered that his health was good until a month before his death when he contracted an illness whose main symptoms were general weakness and cough. After a week his weight suddenly increased from 150 to 167 lbs., and he saw that his face, hands and legs were swollen. At about the same time a number of small round red spots appeared on his legs, thighs and trunk. The sense of weakness increased, and the edema also persisted in variable degree. He went to a doctor who examined his urine and told him that his kidneys were inflamed. As he grew worse rather than better he came down from the country to San Francisco.

There was pitting edema over the shins and his face and hands were puffy. Over the inner surface of the thighs were scattered small hemorrhagic spots which resembled those of purpura simplex. He was dyspneic and cyanosed. Many coarse and fine râles were heard over the bases of the lungs. The heart was enlarged to the left, and was beating rapidly and forcibly. There was no evidence of arteriosclerosis. The blood pressure was 180 systolic and 120 diastolic.

A twelve hour urine collection had a volume of 625 c.c. and a specific gravity of 1.014. It was cloudy with red blood cells. The number of casts was not large. They were all renal failure casts. The blood urea concentration was 363 mg. per 100 c.c.

In the evening of that day the patient became more dyspneic and during the night remained awake in great respiratory distress. In the morning he began to cough up frothy blood, and died with all the evidences of acute pulmonary edema.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found an adhesive fibrous pericarditis, healed apical tuberculosis of the lungs and a local arteriosclerosis of the coronary arteries. A terminal bronchopneumonia was also present.

The kidneys were slightly enlarged, measuring 13 × 7 × 5 cm. each. Their capsules stripped fairly easily leaving a fairly smooth surface which was yellowish

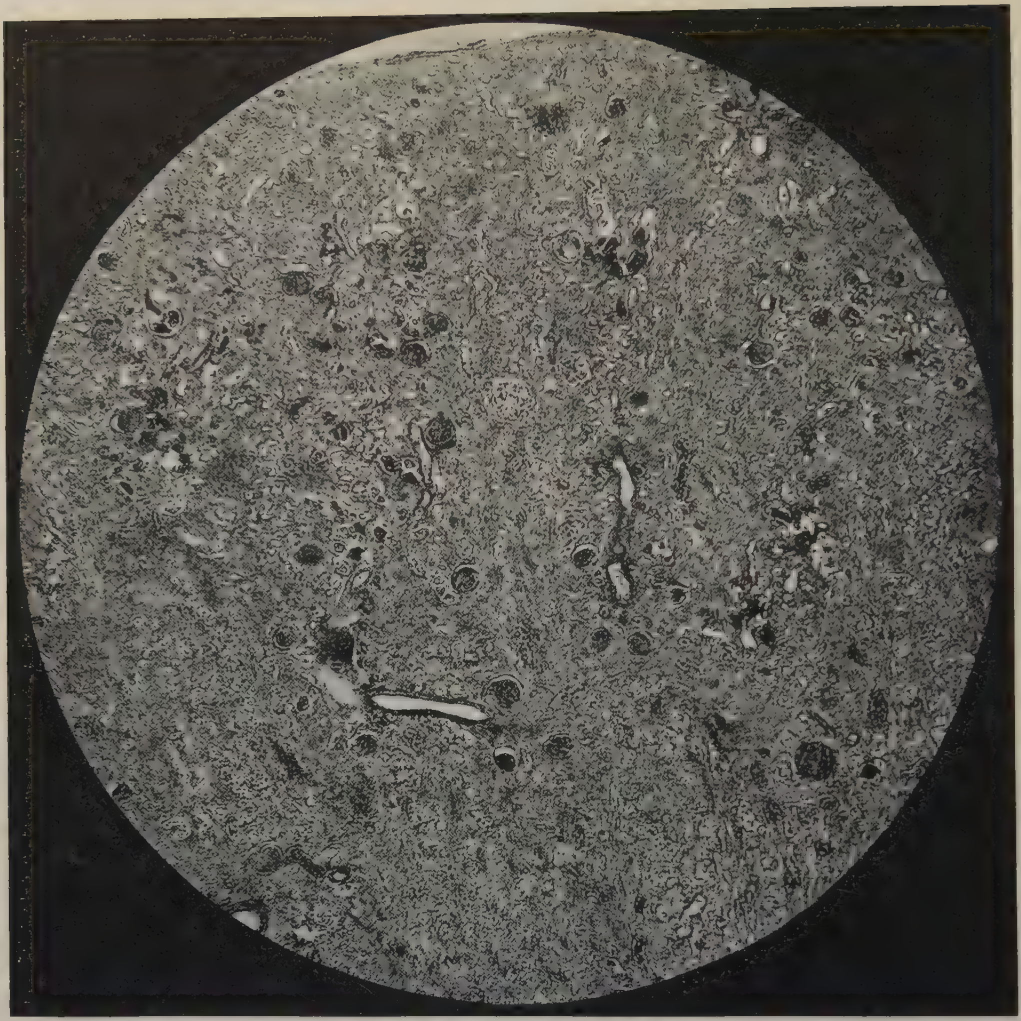

PLATE IV A

There is a very marked proliferation of the connective tissue of the framework of the kidney with an extreme diffuse round cell infiltration of it. The glomeruli are reduced in number and those which remain show varying degrees of fibrosis. Some small branches of the renal artery are definitely thickened.

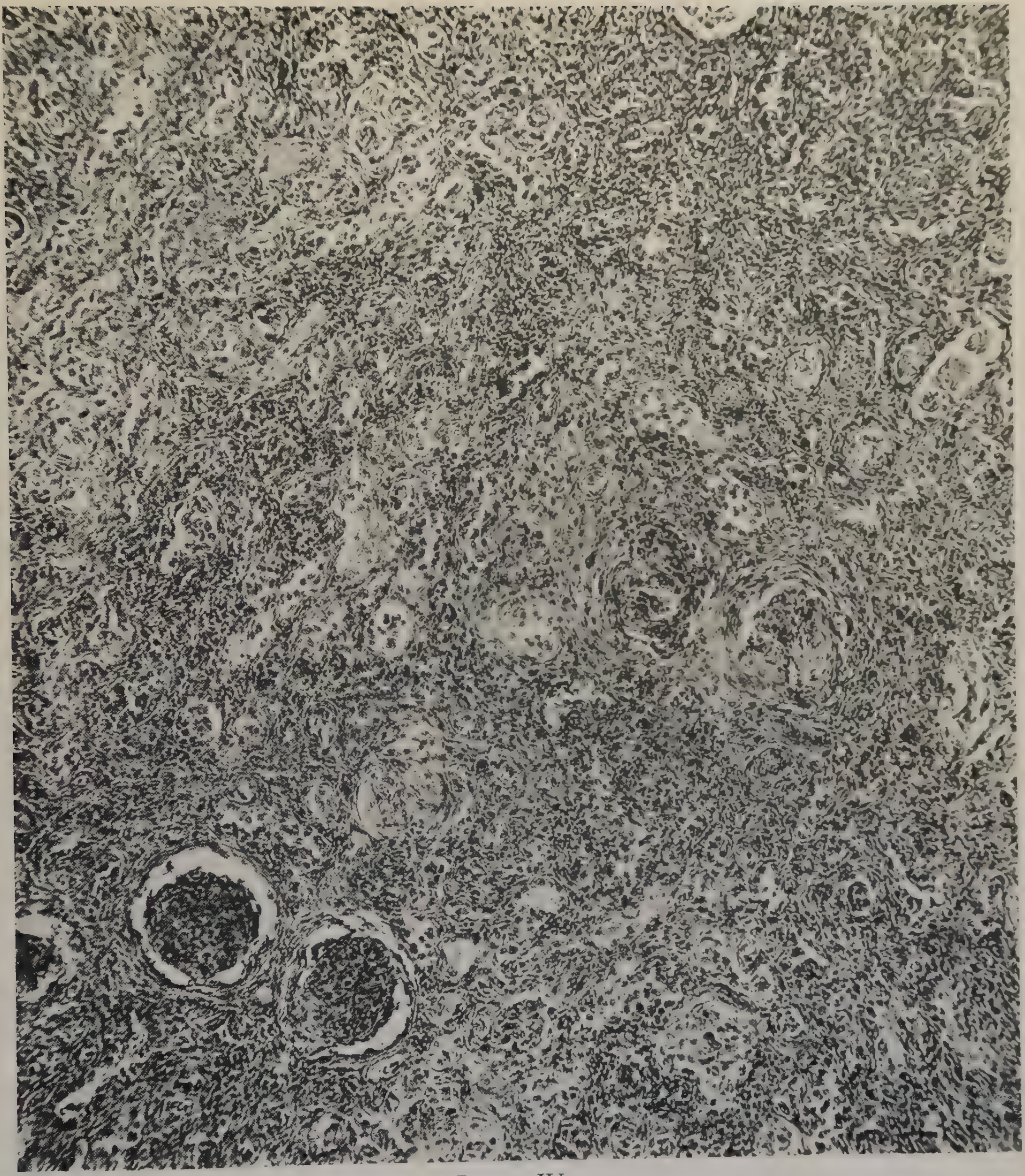

Plate IV b

The kidney structure is almost completely obscured by a heavy leucocytic infiltration and a proliferation of the interstitial tissue. The remnants of compressed tubules with desquamated epithelium may be made out. The glomeruli are shrunken and fibrous.

pink in color. No gross hemorrhages could be seen. On the cut surface they presented a swollen cortex, but no other significant lesion. The renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all the glomeruli show inflammatory lesions of varying degrees of severity and age. In some the tuft is distended with a cellular infiltration of leucocytes, both lymphocytes and polymorphonuclears. In the majority there is also a considerable development of connective tissue which obliterates a portion or in some cases all of the tuft. Lesions of an extracapillary type are also present, varying from an exudate of fibrin and leucocytes into Bowman's space to the production of cellular crescents, adhesions and fibrosis.

Tubules. All of the convoluted tubules are abnormal. These changes range in degree from an extreme cloudy swelling to necrosis and desquamation. Groups of such cross sections, evidently from one tubule unit, are scattered through the cortex. Fatty degeneration, also focally distributed, is frequent. Other tubules show reparative processes. They are lined with an irregular layer of regenerated cells which are arranged in irregular masses which often obliterate the tubule lumen. In the areas of fibrosis there are also present collapsed tubules with atrophied epithelium. The convoluted tubules contain many casts of all sorts, blood cells and blood casts, and in some places great numbers of desquamated epithelial cells. In the collecting tubules are many renal failure casts.

Interstitial Tissue. There is an irregular proliferation of the interstitial tissue throughout the cortex. Scattered through this tissue is an extreme infiltration with leucocytes. Most of these cells are lymphocytes, though polymorphonuclears are also found. In many places sufficient collagen has formed to produce definite scars which obliterate the enclosed glomeruli and tubules.

Arteries. The arteries throughout the kidney present a moderate thickening of their walls.

SUMMARY

The kidney shows an active inflammatory lesion in the glomeruli and interstitial tissue. All types of lesions are present from very early to old stages of the process. There are also extensive epithelial lesions, varying from recent changes, including death of the cells, to reparative regeneration. The arteries are thickened.

Case v

Helen F. Aged sixteen.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Etiology. Unknown.

Duration. Three and one-half months?

Course. Edema was the first symptom which continued until death from uremia.

RELEVANT CLINICAL DETAILS

In this patient only one specimen of urine was examined six weeks after the onset of the edema. It had a dark mahogany color, and the sediment consisted mainly of red blood cells. Blood casts, as well as epithelial, granular and hyaline casts were found. No adequate history was obtained. There was general anasarca with fluid in both pleural cavities and in the abdomen. The heart did not appear to be enlarged. The blood pressure was 125 systolic and 95 diastolic. The patient was taken to another hospital. It was reported that there she had a sore throat and fever and later suffered from blurred vision and severe headaches. The edema increased, and during the last week of life there were several convulsions.

PATHOLOGICAL OBSERVATIONS

At autopsy a diffuse bronchopneumonia with beginning abscess formation was found involving the right lung. There was also an extensive caseation of the peribronchial lymph glands with old healed lesions at the apices of both lungs. The heart was not enlarged. Both the peritoneal and thoracic cavities were filled with clear fluid and there was a considerable edema of the legs. Smears of the lung showed many gram-positive diplococci and polymorphonuclear leucocytes. Both kidneys were essentially the same in appearance. They were of normal size, measuring 14 × 6 × 6 cm. The capsule stripped easily, leaving a smooth and rather pale surface in which no hemorrhages could be seen with the naked eye but which was studded with minute yellow spots. The cut surface showed a marked opacity and widening of the cortex and in the inner zone of the cortex, thin yellow streaks. The pelvis and renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus examined is involved to about the same degree. The lesion consists of a subacute glomerulitis with both intracapillary and extracapillary involvement. The vascular tuft is infiltrated with leucocytes including polymorphonuclears, there is considerable fibrosis between the capillaries and Bowman's space is filled with organized exudate. In many there is a marked proliferation of the capsular epithelium.

Tubules. The convoluted tubules in the cortex are distinctly irregular in size, this in part due to compression by the increased interstitial tissue, but more to the

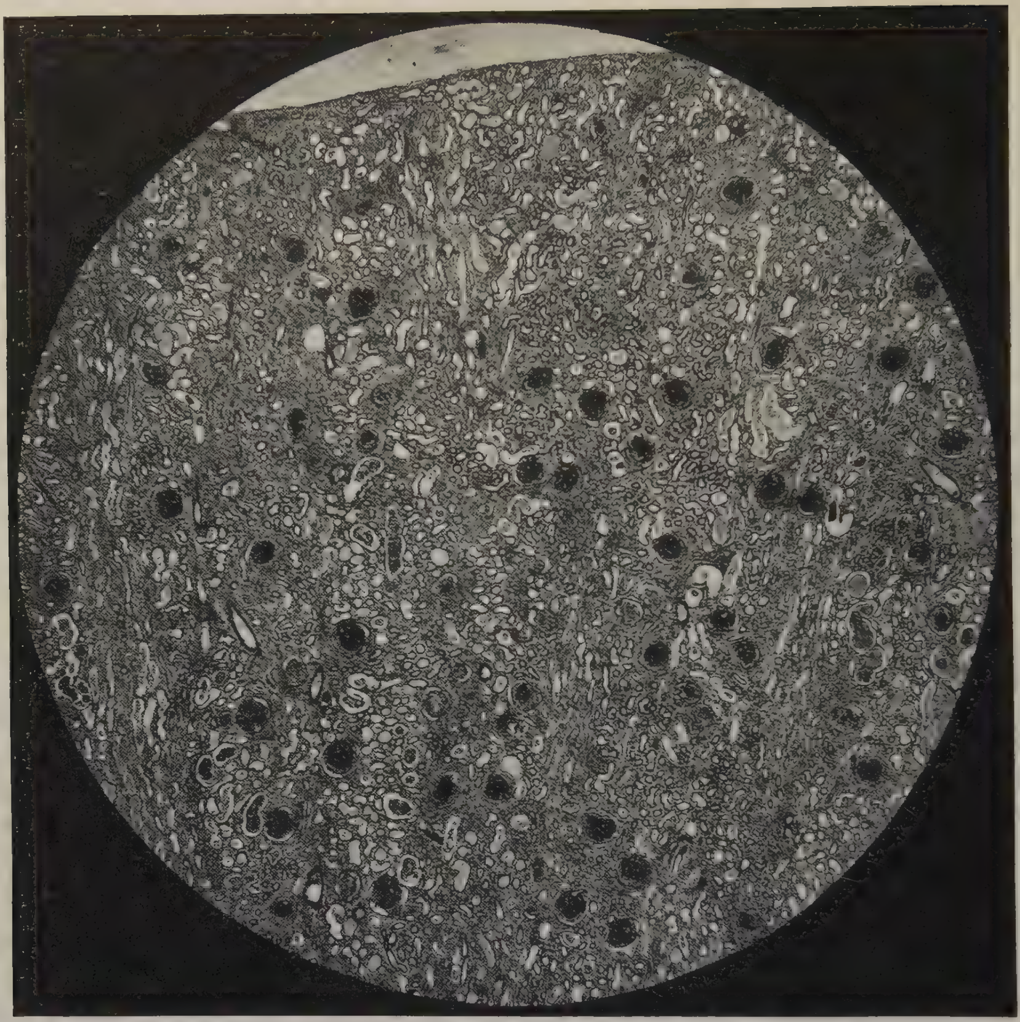

PLATE V A

The glomeruli stand out very prominently as a result of the active inflammatory lesions in them. There is a moderate evenly distributed proliferation of the interstitial tissue with beginning tubular atrophy or dilatation.

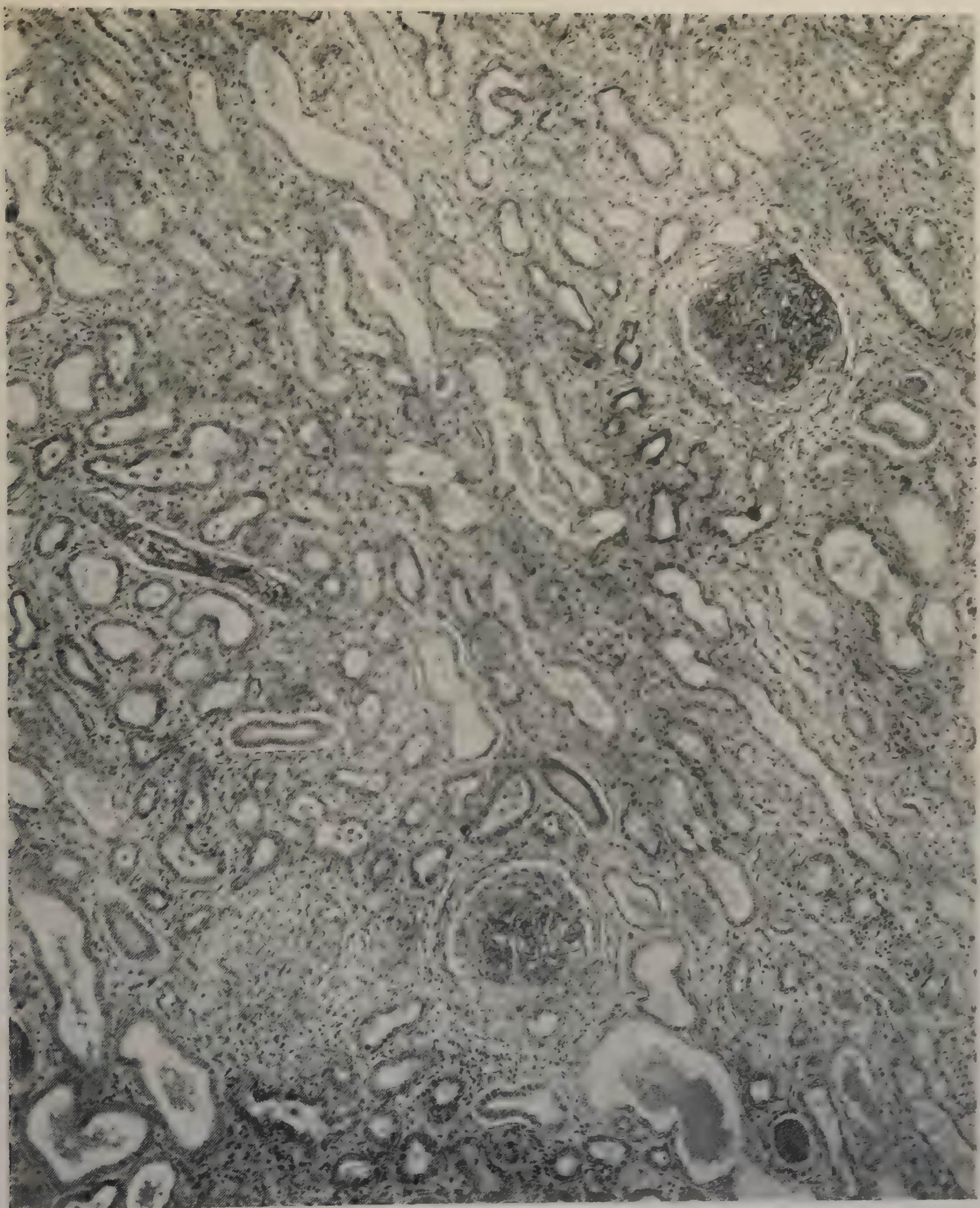

Plate V b

Both the capsular space and the tuft of the glomeruli is involved by the inflammatory process. Throughout the interstitial tissue there are both inflammatory infiltration with leucocytes and proliferation of connective tissue. The tubules are distorted by these changes and are lined with atypical regenerated epithelium.

change in their lining epithelium. This is of the regenerated type, the cells are small and irregular in shape with relatively large and prominent nuclei. In some there is a marked excess of nuclei and cells. In most places the cells are well preserved but isolated areas are found just beneath the capsule and in the medullary rays where there is a heavy accummulation of fine fat droplets in their protoplasm. Casts of all types are found in the lumens of all the divisions of the tubules, as well as recently shed blood cells. In the large collecting tubules are large renal failure casts.

Interstitial Tissue. There is a very definite increase in the interstitial tissue. This is due to a leucocytic infiltration with lymphocytes and few polymorphonuclear leucocytes combined with a definite proliferation of the fibrous tissue. In the cortex, where the change is most severe, there is a considerable compression and distortion of the convoluted tubules, with dilatation of some of the lumens.

Arteries. The large and small arteries are normal.

SUMMARY

The kidneys show a well-advanced glomerulitis with beginning proliferative changes in the interstitial tissue. The activity of the process is shown by the polymorphonuclear infiltration of both these elements of the kidney tissue, and by presence of glomerular hemorrhage. The tubules show evidence of repaired epithelium damage with still active fatty changes. The arteries are normal.

CASE VI

Helen G. Aged twenty.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Etiology. Mastoid infection.

Duration. Eight years. Observed during the last two and one-half years.

Course. The initial stage developed immediately after a mastoid operation. Albuminuria persisted for nearly a year and was then supposed to have disappeared. But six years later an active stage supervened which continued for two and one-half years. The patient died from erysipelas before the terminal stage was fully developed.

RELEVANT CLINICAL DETAILS

In 1914 when she was eleven years old the family physician advised the removal of enlarged tonsils and adenoids although there had been no definite attacks of tonsillitis. After the operation a middle ear infection developed and a mastoid operation was performed. A day or two later considerable amounts of albumin were found in the urine. Unfortunately no specific details as to the condition of the patient or as the nature of the urinary sediment at that time could be obtained, but a diagnosis of nephritis was made and for about a year the diet was restricted. There was a slow convalescence and for a time the child was said to be anemic, but this conclusion was reached on account of her paleness and was not based on blood counts. From time to time the urine was examined for albumin and it was reported that the amount was decreasing until at last it was said to be entirely gone.

During the next six years the girl though not very strong remained free from any serious illness. Throughout this period no urinary examinations were made.

In April 1922 she complained that she became tired more easily than usual and her mother thought she looked pale. This persisted until August when she observed a slight swelling round her ankles and soon afterwards noticed that her face was swollen. She said nothing about this to her parents and it was not until some weeks later that the swelling of the face became apparent to her mother. She was sent to a doctor who found a large amount of albumin in the urine and a considerable number of red blood cells and of white blood cells and epithelial cells in the sediment. The systolic blood pressure was 130. An *x*-ray examination of the chest failed to reveal any cardiac enlargement. Two dead teeth were extracted. She was kept on a milk diet for three months and thereafter on a general diet but without meat. After four months in bed there was a sudden increase in edema without any obvious reason. It was at this time (January 1922) that she was referred for diagnosis and treatment. The patient said she felt perfectly well but there was a generalized edema of all the skin though definite pitting could be obtained only in the legs. A moderate amount of free fluid was present in the abdominal cavity and small amounts in both pleural cavities. There was pronounced pallor but the counts showed only a very slight degree of anemia. The systolic pressure was 120 and the diastolic 90 and the heart did not appear to be enlarged. There was no evidence of arteriosclerosis and no abnormality could be detected in the retinal vessels. No signs of infection were discovered in the throat, sinuses or teeth. Urine cultures were negative.

On January 14, 1922 the twelve hours' night urine after restriction of fluids during the day had a volume of 195 c.c. and a specific gravity of 1.032. It contained 6500 mg. of protein and had an opaque smoky appearance. When a sample was centrifugalized the deposit had a reddish color and occupied a considerable volume. It consisted in the main of red blood cells and white blood cells and epithelial cells. No counts were made but a large number of casts were found. In 100 casts 5 per cent were epithelial and 95 per cent were hyaline casts studded with fat droplets. A considerable number of free fat droplets were also seen. Many of these both within and outside of the casts were doubly refractile. It is evident from these findings that very active inflammatory and degenerative processes were in process of development in the kidneys. Nevertheless the functional capacity at this time was intact for under the strain imposed by taking 30 gm. of urea and large amounts of water the average ratio value was 98 per cent of the amount to be expected from a girl of her size. It may be noted also that in spite of the edema the volume of urine rose to 498 c.c. per hour during the test, an amount well within the range of normal variation.

The edema disappeared on a diet in which sodium was rigidly restricted and which contained an amount of protein sufficient for maintenance and for restitution of the considerable amounts daily lost in the urine. From a purely symptomatic point of view the results were good, for the girl considered that she was regaining her health up to the very end. During her last year she was able to drive a car and lead a fairly normal and enjoyable life. In actual fact she was steadily losing ground.

Table xxi

Cardiovascular Reactions in Case vi

Date	Basal conditions			Daytime conditions			After exercise		
	Syst.	Diast.	Pulse	Syst.	Diast.	Pulse	Syst.	Diast.	Pulse
1922 Jan.....	110	90	100	120	90				
May....	118	90	89	110	90	116	145	100	148
Sept.....	112	96	104	110	90	118	160	105	116
1923 Jan.....	136	100	88	136	106	128	156	105	156
March ..	136	106	86	150	100	140	150	95	148
June....	142	98	100	145	100	130			
Sept.....	140	100	82	145	100	104	140	90	120
1924 Jan.....	...	...	...	140	100	100	150	75	140

There was a progressive anemia which however never became extreme. The lowest red cell count was 2,500,000. During the last six months there was a loss of 20 lbs. of body weight, though she never developed any gastrointestinal symptoms and took an ample amount of food to the end. The *x*-ray gave evidence of a gradual increase in the size of the heart, but no appreciable change in the size of the kidneys was detected. The successive blood pressure and pulse rate measurements are collected in Table xxi. They show a definite tendency to a rise in the blood pressure levels.

The gradual change in the urinary sediment as the terminal stage was approached is shown in Table xxii by the appearance and increase in the number of renal failure casts. The rates of cast, cell and protein excretion are given in Table xxiii.

Table xxii

Differential Cast Counts (Case vi)

Date	Blood, per cent	Epith., per cent	Gran., per cent	Fatty, per cent	Waxy, per cent	Hyal., per cent	Renal failure, per cent
1922 Jan.	0	5	0	0	0	95	0
May	0	23	7	1	7	62	0
Sept.	0	11	3	6	1	79	0
1923 Jan.	0	7	3	5	2	69	14
March	0	4	4	8	4	30	50
June	0	4	4	6	0	70	16
Sept.	0	0	3	0	0	19	78

Table xxiii

Rates of Cast, Cell and Protein Excretion (Case vi)

Date	Casts	R.B.C.	Ep. and W.C.	Protein	Vol.	Sp. Gr.
1922 Jan.	+	+	+	6,500	194	1.032
April	693,000	+	+	7,600	365	1.027
Sept.	350,000	Smoky	+	8,200	410	1.021
1923 Jan.	3,622,000	+	+	6,100	610	1.017
March	402,000	+	+	5,300	505	1.018
June	112,500	1,142,000	4,500,000	3,600	390	1.016
Sept.	647,000	9,840,000	8,900,000	3,300	454	1.013
1924 Jan.	1,390,000	10,600,000	5,900,000	1,140	321	1.014

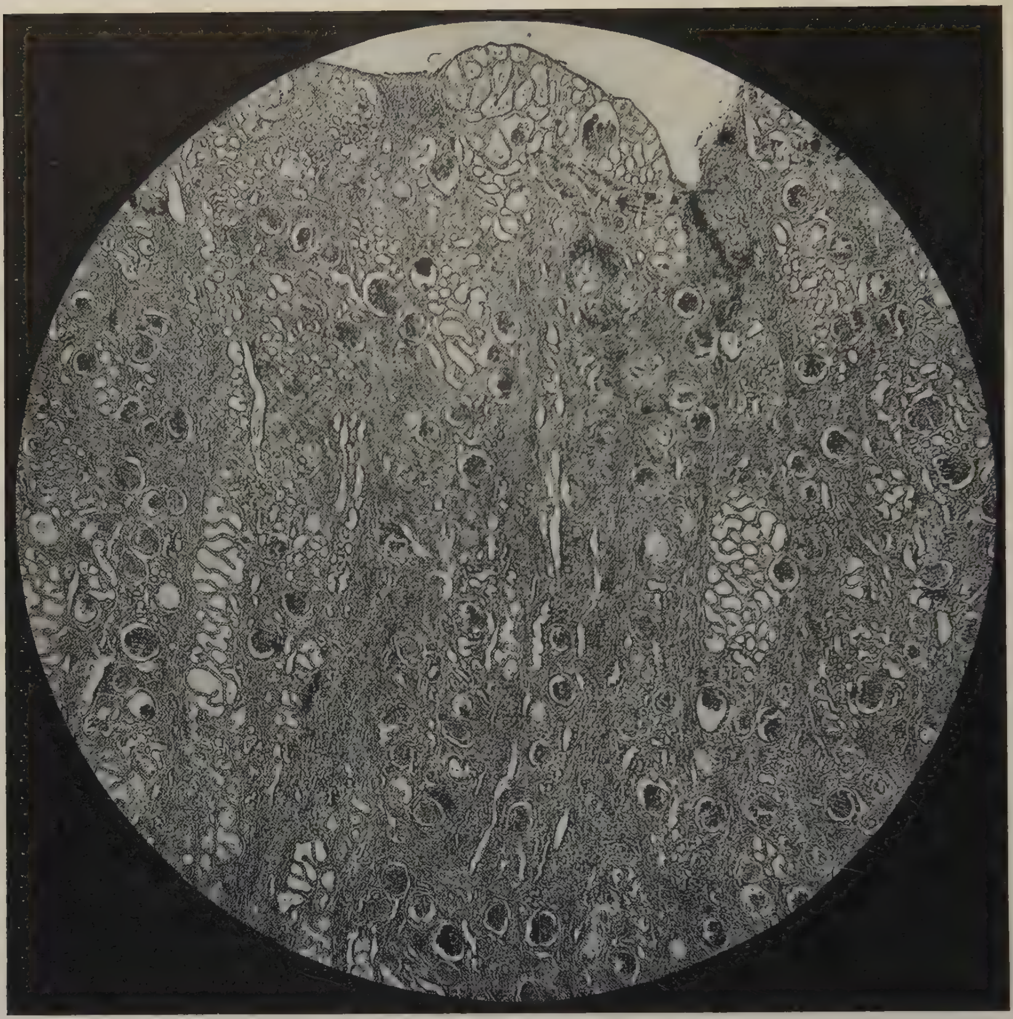

PLATE VI A

There is a very marked inflammatory proliferation of the interstitial tissue with heavy round cell infiltration. As a result the architecture of the kidney is altered. The glomeruli are in various stages of inflammatory destruction. Clusters of dilated and hypertrophied tubules alternate with areas where the tubules are collapsed.

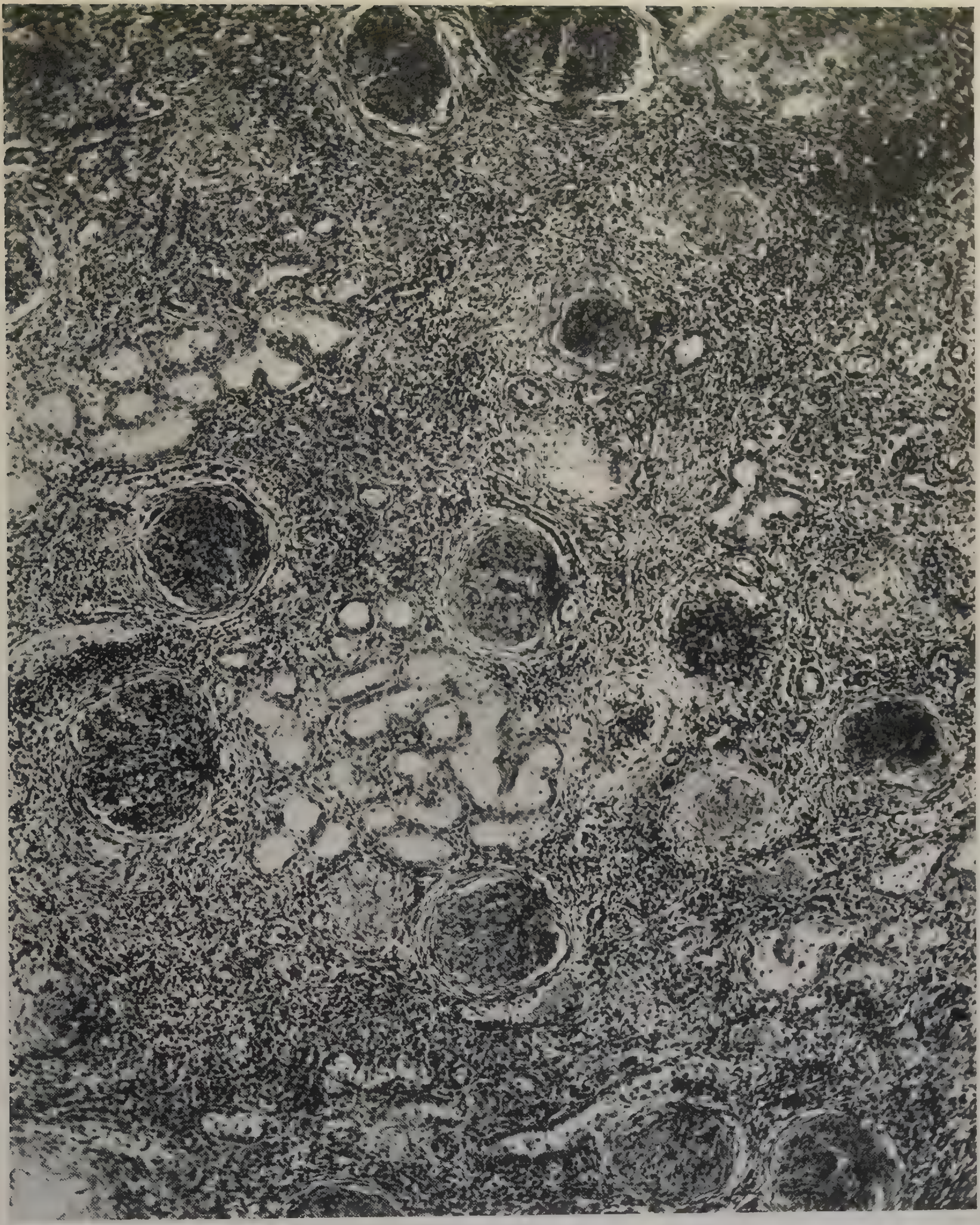

PLATE VI B

Throughout the interstitial tissue there is an intense infiltration with leucocytes, chiefly of the round cell type. As a result the tubules have been displaced in large areas. The glomeruli are also infiltrated with these cells and there is some fibrous thickening of their capsule.

The progressive decrease in the amount of functioning renal tissue is shown graphically in Figure 19.

The patient died three months after the last examination. She had been feeling well and happy and going to a good many parties until she contracted a cold in the head from which a bronchitis developed. The next day erysipelas appeared and three days later she died. The physician who was in charge at this time reported that the urine volume was 1100 c.c. for a twenty-two hour period just before the end. Six hours before death there were three separate "convulsive attacks" each of which continued for fifteen to twenty minutes. Unfortunately no blood was obtained but there was undoubtedly pronounced nitrogen retention since the blood urea concentration had been gradually increasing during the past year and three months before had reached a level of 125 mg. per 100 c.c. Whether the "convulsions" were more than marked muscular twitchings is uncertain.

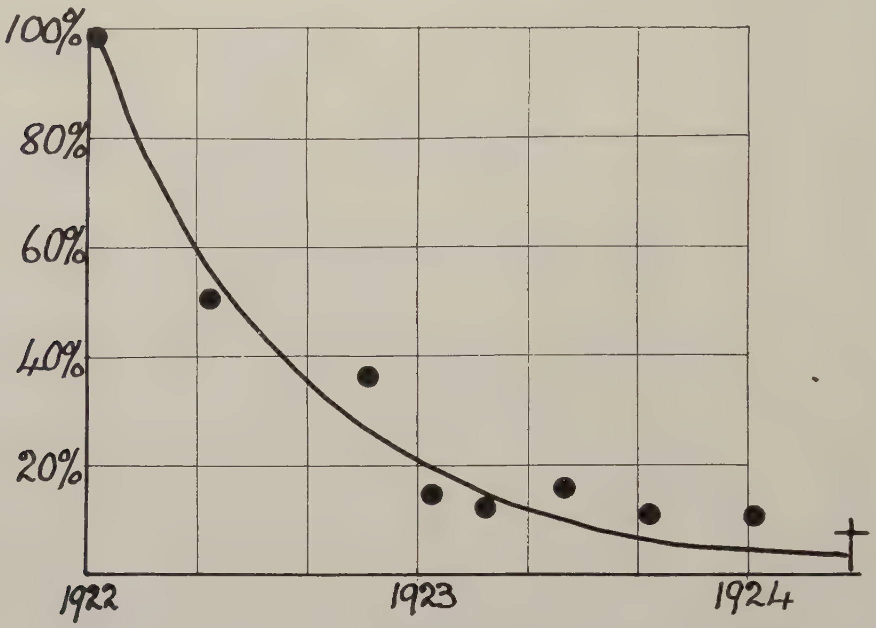

FIG. 19. Amount of renal tissue, Case VI.

PATHOLOGICAL OBSERVATIONS

Only the kidneys could be examined post mortem. They were of almost normal size, measuring 11 × 5.5 × 3.5 cm. The capsule was somewhat adherent and when stripped left a pale yellowish very fine granular surface on which no gross hemorrhages could be seen. The cut surface showed the same discoloration. The arteries were not abnormal.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus examined in many sections shows inflammatory lesions of different degrees of activity. The lesion in all is of the intracapillary type, consisting of leucocytic infiltration of the glomerular tuft and in many instances of capillary thrombosis. There is very little exudate in the capsular space though capsular adhesions are frequently found. Many of the glomeruli show fibrosis varying from small amounts of fibrous tissue to an almost complete obliteration of the glomerular tuft and space with a hyaline mass of collagen.

Tubules. The convoluted tubules and broad ascending limbs of Henle's loop are markedly affected by the proliferation of the interstitial tissue. In the greater part of the cortex they show an almost total atrophy, consisting of small groups of compressed and distorted epithelial cells with little or no lumen. Scattered among these larger fibrosed areas are isolated groups of tubules whose epithelium is tremendously swollen, the cells being filled with granules and hyaline droplets. Occasionally one finds groups of tubules whose epithelium shows a fatty degeneration. In many of these tubules there is definite necrosis and desquamation of the epithelium and often an accompanying marked regeneration so that the lumen of the tubule is almost completely filled by the proliferating cells.

In the lumen of the convoluted tubules there is a large amount of detritus, remnants of epithelial cells, granular material and even red blood cells. This is usually not consolidated in the tubules of the cortex, but the straight tubules and particularly the large collecting tubules and ducts of Bellini are distended with typical large renal failure casts.

Interstitial Tissue. There is a marked increase in the interstitial tissue of the cortex, but the increase is due chiefly to an extreme cellular infiltration with lymphocytes rather than to the formation of definite collagen. This interstitial thickening has produced the severe atrophy and distortion of the majority of the convoluted tubules which were described previously. The connective tissue of the medulla is also definitely increased and here also definite round cell infiltration is seen, though to a very much less degree.

Arteries. The larger arteries show no very definite lesions, though around many of them the leucocytic infiltration of the interstitial tissue is more intense than elsewhere.

SUMMARY

The kidney shows active lesions in all its elements; a severe glomerulitis of the intracapillary type, extreme tubular degeneration and intensive cellular infiltration and some fibrosis of the interstitial tissue. As a result the architecture of the kidney is considerably altered. Renal failure casts are present in the larger collecting tubules.

Case VII

Henry G. Aged six.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Two years and eight months. Observed during the last year and nine months.

Etiology. No information.

Course. In August 1924 edema of the face and feet appeared and gradually but steadily increased. There was no knowledge of any preceding illness. When seen in July 1925 the urinary findings suggested a glomerular nephritis but with an active degenerative process superadded. During 1926 the edema almost disappeared but there was no obvious change in the condition of the kidneys. On April 20, 1927, he was brought from the country with pneumonia and died a few hours after admission.

RELEVANT CLINICAL DETAILS

Edema was the only symptom and it developed slowly and independently of any preceding infection during August 1924. In February of that year it is true the child had had measles but the attack was mild and did not seem to have any effect on his general health. Even after the edema of his face and legs had become pronounced he seemed to be quite happy, played much as usual and ate and slept as well as before. His mother watched him closely at this time and is sure that the urine was never brown or red. She took a specimen to a doctor soon after the edema has made its appearance and saw that it solidified when it was boiled.

The edema remained in varying degree but never in sufficient quantity to inconvenience him greatly until April 1925. During that month his abdomen became very tight and 2 quarts of milky fluid were removed. By July 1925 the fluid had collected in still larger amount and 8 quarts were withdrawn.

He was first seen towards the end of July 1925. There was a generalized subcutaneous edema and a moderate amount of free fluid in the peritoneal cavity. The arteries did not seem to be thickened nor the heart enlarged. The retinal arteries showed no abnormality. The blood pressure was 105 systolic and 80 diastolic. There was no anemia. A red blood cell count gave 4,520,000 per cubic millimeter. Fluid withdrawn from the peritoneal cavity looked like watered milk, and contained only 0.1 per cent of protein. The blood urea concentration was 27 mg. per 100 c.c. The plasma looked like milk.

This history and these observations conform to the condition described by Volhard and Fahr as "genuine nephrosis" and a merely qualitative examination of the urine would have confirmed this diagnosis. At the first examination 296,000 casts per twelve hours were found. Of these 4 per cent were epithelial, 4 per cent were fatty and 92 per cent were hyaline. All of these casts were sprinkled over with fat droplets. The number of white blood cells and epithelial cells was 9,600,000 per twelve hours and among them were many epithelial cells containing droplets ("oval fat bodies"). The rate of protein excretion was 1750 mg. per twelve hours. However, a careful count disclosed the presence of 1,860,000 red blood cells. These were all lyzed and were really the stromata of red blood cells. The child was losing edema fluid and the specific gravity of the urine never rose above 1.015, so that it seemed probable that many red blood cells had been completely dissolved. This consideration led to the diagnosis of a hemorrhagic lesion with a superadded fatty degeneration.

The edema rapidly subsided but the patient went back to the country before a satisfactory concentration of urine was reached. A thorough examination failed to disclose any infection in the sinuses or elsewhere. The tonsils were somewhat enlarged but as there was no history of tonsillitis, it was decided not to remove them until his nutrition had improved.

He was not seen again until August 1926 and then only for a few hours. He was much improved in his musculature and general nutrition but he still had occasional edema of the legs and face. There was no ascites. He had been free from infection with the exception of two slight colds in the head which had lasted for a few days only. His blood pressure was 100 systolic and 75 diastolic. The urine still contained much albumin but was too dilute for sediment examination. On April 19, 1927, he was brought down from the country in a moribund condition. He had the typical respiration and appearance of a child with pneumonia. The condition had commenced suddenly on April 15 with sharp epigastric pain, vomiting and dyspnea. He died early on April 20 a few hours after admission to the hospital. Unfortunately no urine was collected. The blood urea concentration was 183 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a secondary anemia, a bronchopneumonia, ascites and hydrothorax. There were also some fatty streaks in the aorta as well as a fatty liver. The kidneys were not enlarged, their capsules stripped easily leaving a smooth surface which was somewhat congested. The cut surface showed some swelling and opacity of the cortex. No definite hemorrhages were seen. The pelvis and arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus studied is the seat of a very active inflammatory process. The involvement is both intracapillary and extracapillary. The tufts are enlarged, infiltrated with round cells and polymorphonuclear leucocytes and the capillaries are filled with fibrin thrombi in which there is nuclear debris from necrosis of the endothelial cells. Bowman's space contains granular material and exudate and in some places definite crescents and adhesions are seen. Connective tissue development, both within the tuft and about it, is only moderate in amount.

Tubules. The convoluted tubules of the cortex are markedly deformed by proliferating interstitial connective tissue. Some are compressed and flattened; others

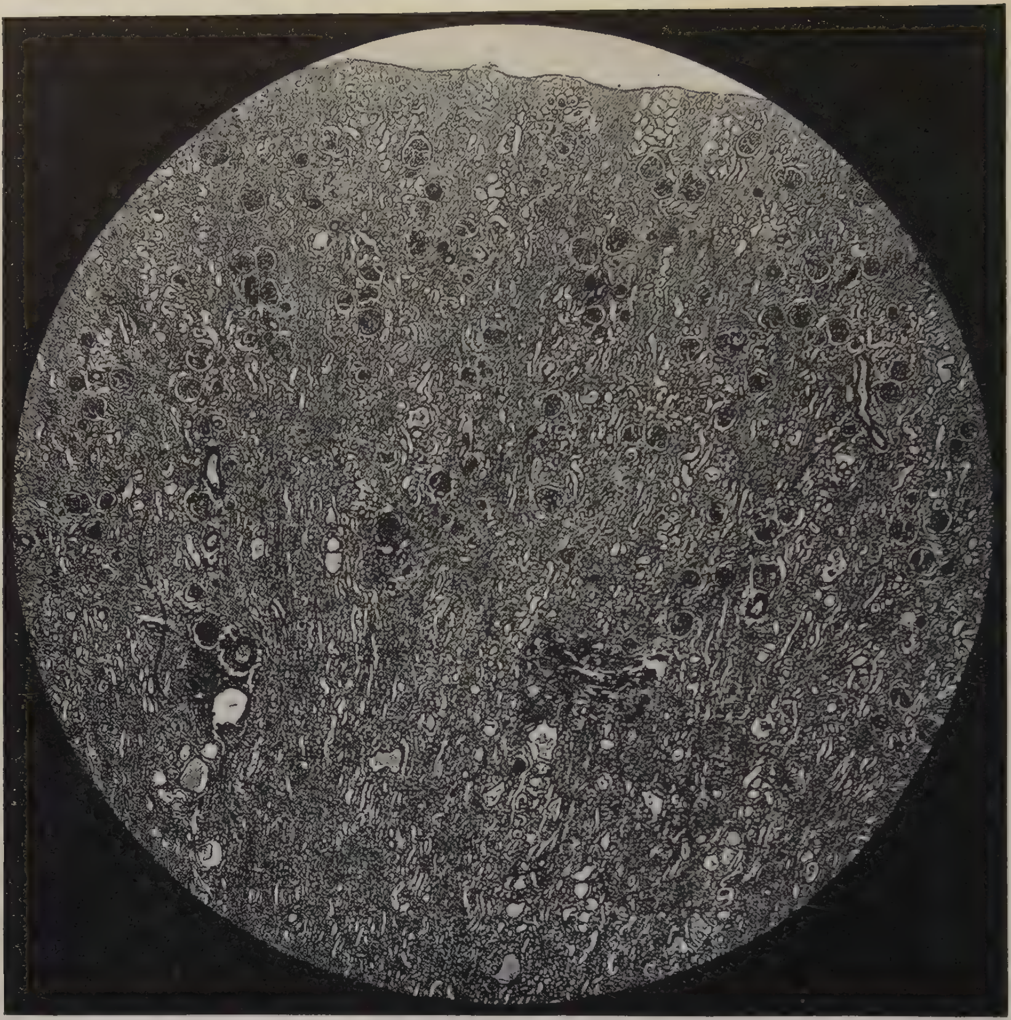

Plate VII a

The glomeruli stand out as dark structures as a result of various stages of the inflammatory process. There is a moderate evenly distributed inflammatory proliferation of the connective tissue with considerable tubular atrophy. Patches of intense round cell infiltration are scattered through the section.

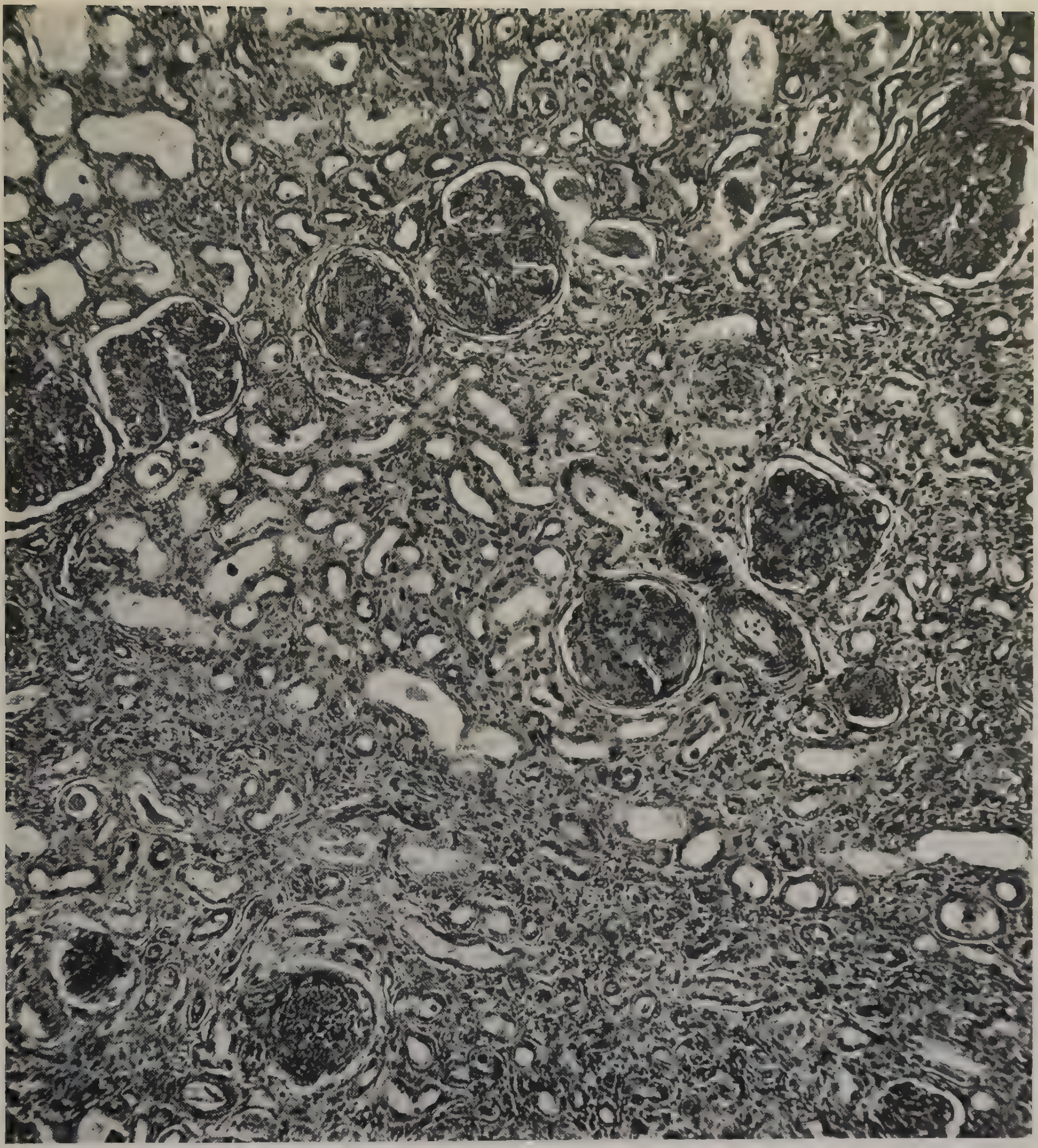

PLATE VII B

In all of the glomeruli the active inflammatory processes are apparent. In the interstitial tissue leucocytic infiltration and connective tissue proliferation have compressed the tubules. The epithelium of the latter is replaced by that of the irregular regenerated type. (Cf. Plate XCI.)

are dilated and their lumens filled with granular material. The epithelium is either atrophied in the collapsed tubules or of the regenerative type, masses of large oval nuclei filling the lumen in some cases. In the dilated tubules the epithelium is flattened, though others of these large tubules have a lining of cells which are definitely larger than normal. Scattered among these tubules are others, particularly in the lower layers of the cortex, whose epithelium shows extreme cloudy swelling and necrosis with desquamation. The tubules contain throughout debris or formed casts of all types. There are large renal failure casts in the ducts of Bellini.

Interstitial Tissue. Throughout the cortex and extending down into the outer layers of the medulla is a diffuse proliferation of the interstitial connective tissue. In these proliferating tissues are areas of marked leucocytic infiltration with cells of both the mononuclear and polymorphonuclear type. The developing connective tissue compresses the tubules or separates them widely from each other. In some areas near the free surface of the kidney beginning retraction of scar-like areas is seen.

Arteries. There are no observable lesions in any of the arteries.

SUMMARY

The kidneys show a very active inflammatory process in the glomeruli, with severe degenerative and reparative changes in the tubular epithelium. There is sufficient connective tissue proliferation to affect the architecture of the kidney moderately. The arteries are normal.

CASE VIII

Alparata H. Aged thirty-eight.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Unknown.

Etiology. No information. Terminal streptococcus viridans septicemia.

Course. Since 1900 the patient had been short of breath on exertion. There had been numerous attacks of tonsillitis. In 1911 she was told that she had heart disease. Since April 1925 there had been a progressive loss of weight and strength, cough and night sweats. On admission to the hospital on October 27, 1926, she was found to have a fever, anemia, many petechial hemorrhages, a palpable spleen and a markedly enlarged heart with evidences of mitral stenosis and of aortic regurgitation. The blood pressure was 100 systolic and 60 diastolic. A streptococcus viridans was grown from a blood culture.

On November 4 a concentration test was carried out. The volume was 555 c.c. per twelve hours, the specific gravity 1.019. The rate of protein excretion was 857 mg. for the twelve hour period. The number of casts in twelve hours was 296,000, of red blood cells 192,000,000, and of white blood cells and epithelial cells 15,000,000. All of the casts were of epithelial origin though only a small percentage were broad.

These are not the results which are found in the usual case of the "embolic nephritis" which has been described in subacute endocarditis. Since it seemed unlikely that the septicemia alone could have been responsible, a diagnosis of a diffuse and not a merely local renal lesion was made.

The patient died four days later. Unfortunately the level of the blood urea concentration was not determined.

PATHOLOGICAL EXAMINATION

At autopsy numerous small petechiae in the skin were found. The heart was about twice normal size. The flaps of the aortic and mitral valves were fibrous and shrunken and along their edges were masses of recent soft thrombus in which were found gram-positive diplococci. In the spleen were two fairly recent infarcts.

The left kidney was normal in size. Its capsule stripped easily, leaving a smooth, mottled red and grey surface in which were a few scattered petechial hemorrhages. On the posterior surface was a recent infarct. The cut surface shows a very opaque and somewhat narrowed cortex. The right kidney was the same as the left, and also contained a recent infarction.

The arteries of the various organs were normal, and except for a general passive congestion of the viscera no significant gross lesions were found.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all the glomeruli are involved in the active stages of a glomerulitis. The glomerular tufts are infiltrated with leucocytes and Bowman's

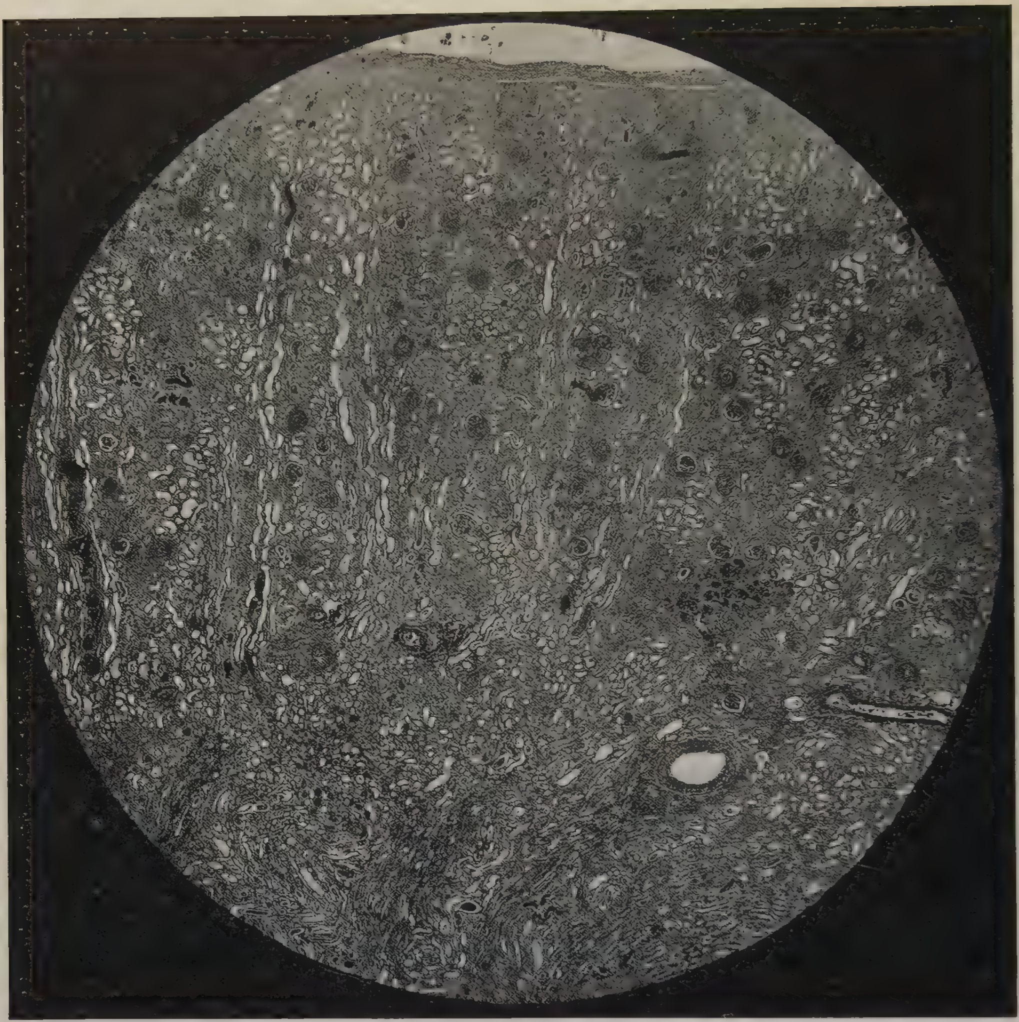

Plate VIII a

The connective tissue throughout the cortex shows an irregular proliferation. As a result clusters of relatively uninvolved tubules alternate with areas of tubular destruction and atrophy. Many of the glomeruli are fibrosed and the remainder show varying stages of inflammation.

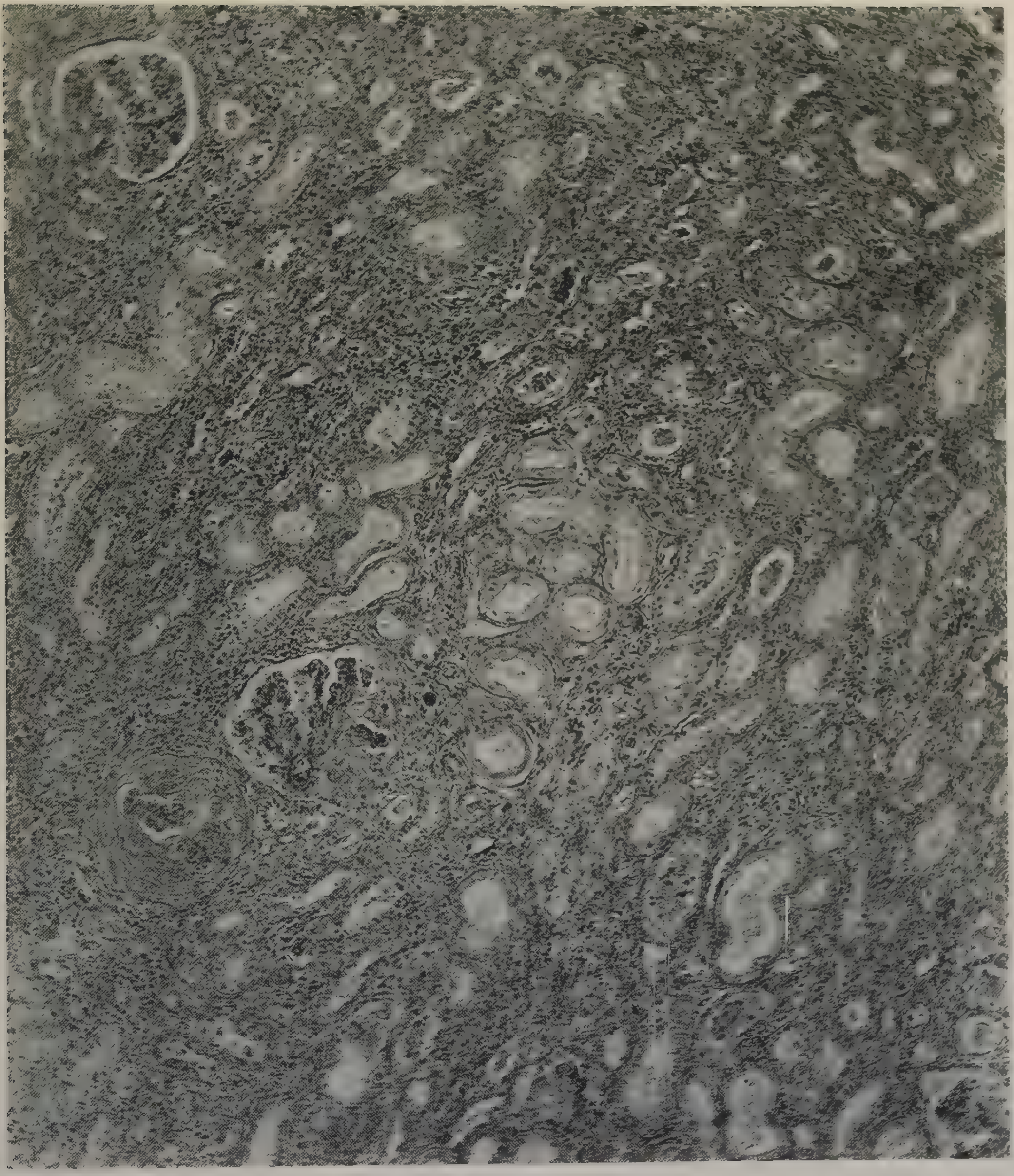

Plate VIII b

The inflammatory process in the glomeruli with obliteration of the tuft is well shown. There is a heavy infiltration of the interstitial tissue, some tubules being collapsed while others persist.

space is filled with an exudate of fibrin and leucocytes. There is considerable proliferation of connective tissue both in the tuft and in the space with the result that the glomeruli show different stages of destruction from an early intracapillary fibrosis to an almost complete obliteration of the entire structure. In most, however, a few capillaries still exist in the tuft. Occasionally a glomerulus can be found in which is a typical focal area of necrosis.

Tubules. Many of the convoluted tubules in the cortex are compressed by the increased interstitial tissue and are lined with a layer of darkly staining atrophic cells. There are other areas in which the tubules are normal in size. Their epithelium is swollen and granular and occasionally is found filled with fat droplets. In others the epithelium is of the irregular regenerated type. The lumens of many of the tubules are dilated and filled with detritus or consolidated hyaline and granular casts. A few are filled with recently shed red blood cells. The broad ascending limbs of Henle's loop show the same lesions. The epithelium of the collecting tubules is normal, but their lumens contain many granular casts.

Interstitial Tissue. Throughout the cortex there is a diffuse proliferation of the interstitial tissue. This is still quite cellular, the nuclei of the fibroblasts being very prominent, as well as those of the leucocytes which diffusely infiltrate it. The latter cells are mostly lymphocytes but there is a considerable admixture of polymorphonuclears.

Arteries. The intima of the arteries shows a slight fibrous thickening but there is no very marked involvement of them, nor any significant perivascular infiltration.

SUMMARY

The kidneys show an actively progressive intracapillary and extracapillary glomerulitis with a cellular proliferation and leucocytic infiltration of the interstitial tissue. There is a moderate degeneration of the epithelium and the arteries are essentially normal.

CASE IX

Eugene McV. Aged twenty-one.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Unknown.

Etiology. Unknown.

Course. The patient had noticed an unexplained weakness in February 1927. Although it persisted he did not consult a doctor until January 1928 when he was obviously anemic. He was seen in February 1928 when the urine showed that he was still in the active stage of an intense hemorrhagic nephritis. By March the blood urea concentration was high and only renal failure casts were found. He died in uremia on April 19, 1928.

RELEVANT CLINICAL DETAILS

There was no history of any former serious illness. In 1921 his tonsils were removed, although he had no recollection of ever having had a sore throat. He was a strong athletic boy and after leaving school was given charge of an outdoor gymnasium and playing field. The first indication he had that anything was wrong was in February 1927 when he found that he no longer had any inclination for playing basketball. But he still had a good appetite and looked well, and it was not until December of that year that his sister was struck by the paleness of his lips. He consulted a doctor in January 1928 because of a slight cough. The urine at that time contained many casts, red blood cells and epithelial cells and much albumin. The blood urea concentration was 75 mg. per 100 c.c. The hemoglobin concentration was 52 per cent.

He was first seen on February 9, 1928. He said that he felt all right and slept and ate well, though he no longer felt inclined for hard physical work. The heart was not enlarged, and the retinal arteries appeared normal. The blood pressure was 125 systolic and 70 diastolic. The blood urea concentration was 69 mg. per 100 c.c. There was no edema.

On February 11 a concentration test was obtained. The volume was 931 c.c. and the specific gravity 1.014. In twelve hours 2010 mg. of protein were excreted. The number of casts was 13,600. Five per cent of these casts were blood casts, 5 per cent granular, 15 per cent waxy and the remainder hyaline. There were no renal failure casts. Many of the casts contained fat droplets and there were numerous "oval fat bodies." The urine was smoky and the red blood cells numbered 615,000,000 per twelve hours. There was evidence also of an intense degenerative lesion for the number of white blood cells and epithelial cells was 50,500,000 and many of these cells showed signs of granular or fatty degeneration. It seemed reasonable, therefore, to conclude that we were observing the urinary evidences of an extreme inflammatory and degenerative renal lesion.

On March 10, without any obvious subjective change and still with a blood pressure continuously within normal limits, another urinary examination revealed

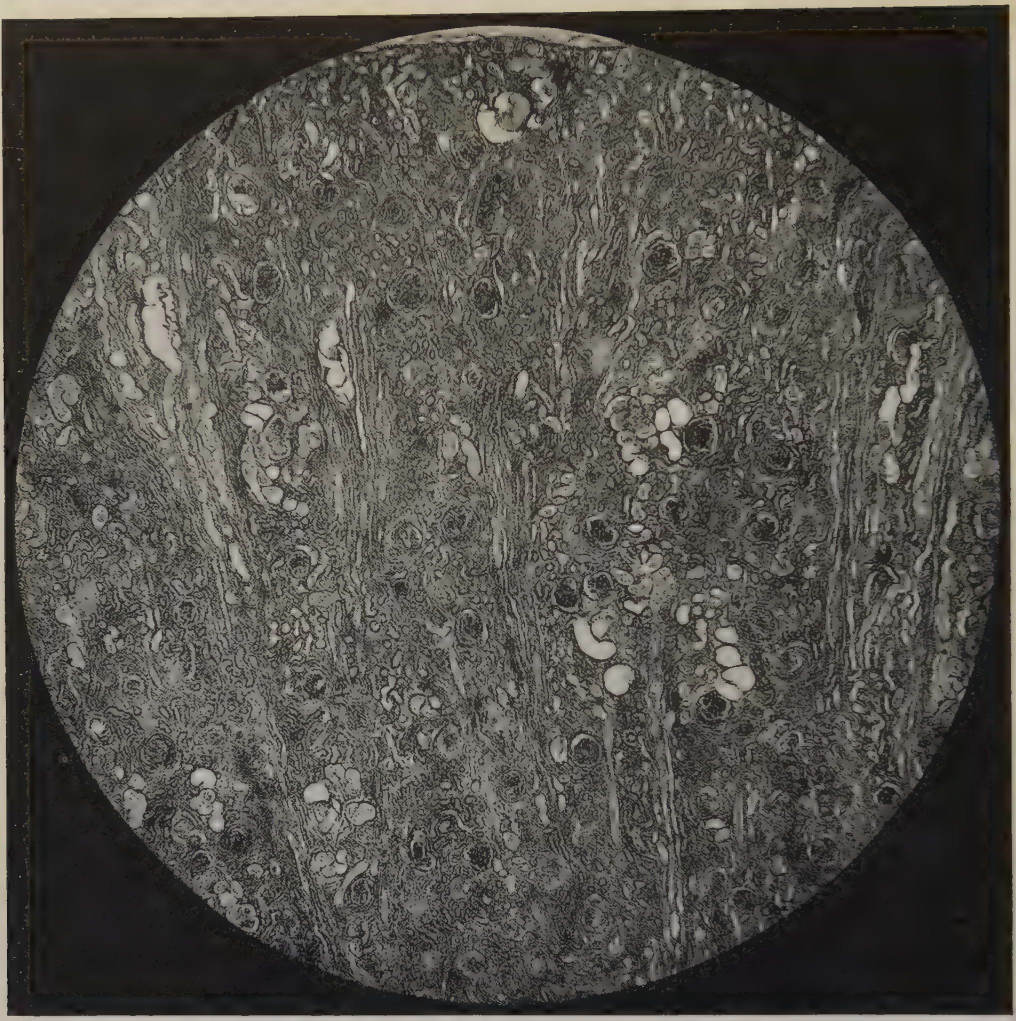

Plate IX a

All of the glomeruli show varying stages of destruction by the inflammatory processes. The tubules are irregularly collapsed and atrophied or dilated and filled with detritis as a result of the inflammatory proliferation and infiltration in the framework of the kidney.

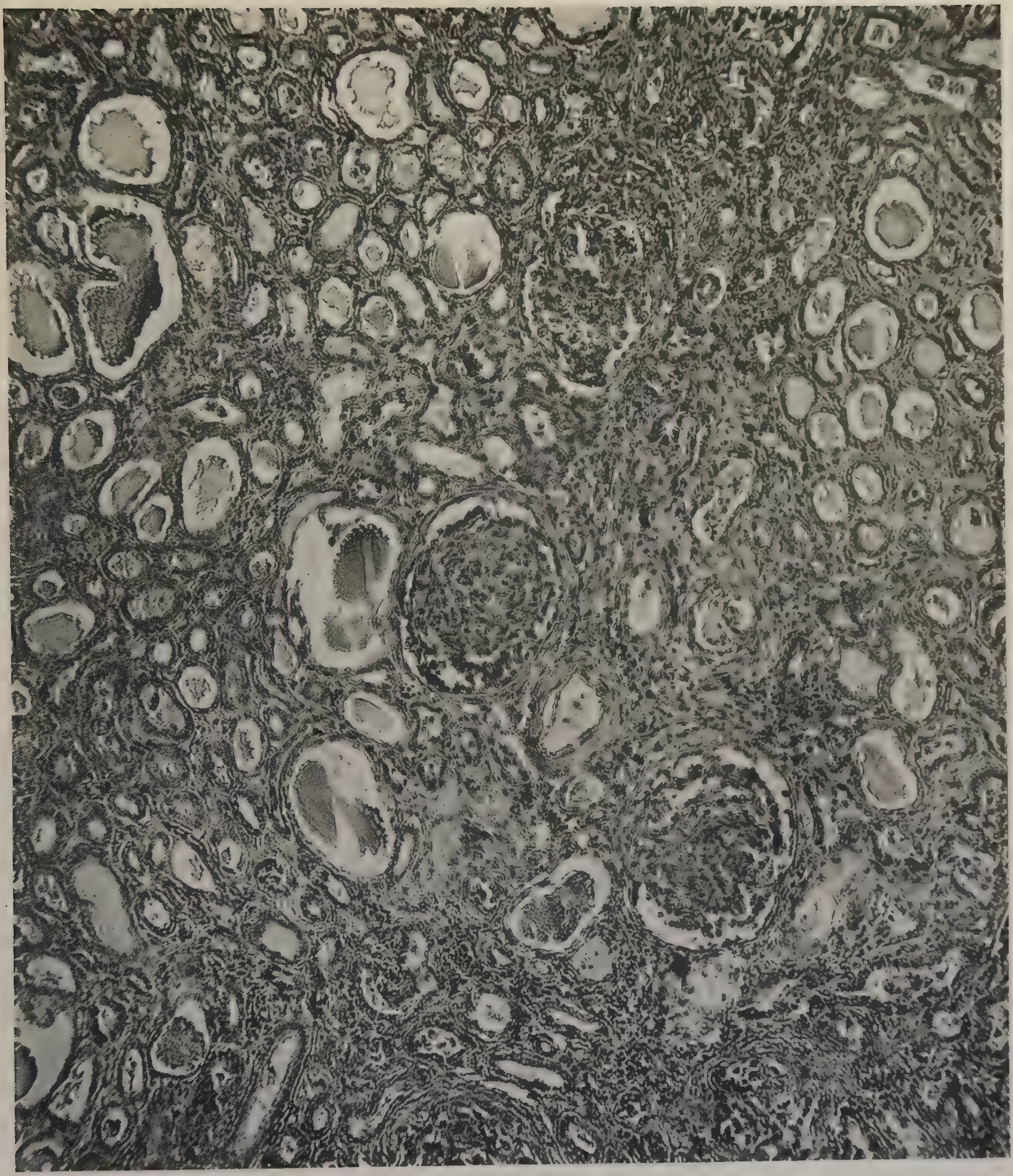

Plate IX b

Bowman's space of the glomeruli is filled with inflammatory exudate. There is a definite proliferation of the interstitial tissue with deformity of the tubules, many of which are filled with casts.

a sediment strikingly different in respect to the nature of the casts. They were now all of the renal failure type. In other respects the figures indicated no subsidence in the intensity of the lesion. The rate of protein excretion was 6835 mg. per twelve hours. There were 81,000 casts. The number of red blood cells was 1,580,000,000 and there were 31,500,000 white blood cells and epithelial cells. On that day it was found that the blood urea concentration had risen to 191 mg. per 100 c.c.

Towards the end of March there was obvious weakness and the blood urea concentration had increased to 216 mgs. per 100 c.c. Several small hemorrhages appeared round the retinal arteries near the discs. The blood pressure rose to 155 systolic and 90 diastolic. By the middle of April there was slight edema, particularly of the face, extreme pallor and muscular twitchings. He passed slowly into coma and died on April 19, 1928.

PATHOLOGICAL OBSERVATIONS

The kidneys alone were obtained at autopsy. They were of normal size. Their capsules stripped easily leaving a fairly smooth surface of normal color, on which a very occasional petechial hemorrhage could be found. The cut surface showed indistinct markings but was otherwise negative. The arteries appeared normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus examined is the seat of an active glomerulitis. The tufts show a definite increase in nuclei, a result of both cellular proliferation and leucocytic infiltration. The capillaries are compressed. Bowman's space contains exudate and in the majority of cases this forms a definite glomerular crescent which further compresses and distorts the tuft. There is a beginning proliferation of connective tissue in both this exudate and in the tuft.

Tubules. The tubules of the cortex are markedly deformed by the changes in the interstitial tissue. Some are collapsed and atrophied, others are dilated and contain hyaline or colloid material. The epithelium in both cases is compressed and atypical in size and shape. Many of the lumens are filled with hyaline casts, and there are also present masses of red blood cells and definite blood casts. Since the tissues were fixed in formalin the latter contain black hemoglobin precipitate and can be easily recognized even when complete lysis of the included red blood cells has occurred.

Interstitial Tissue. There is a diffuse proliferation of the connective tissue throughout the cortex with the formation of collagen and round cell infiltration. In some places the proliferation is particularly dense so that scar-like areas are formed which, when they reach the surface, produce a retraction of the cortex.

Arteries. The arteries are essentially normal. Their intima shows no fibrous thickening. About some of them the round cell infiltration is very dense.

SUMMARY

There is present in the kidneys a subacute but still quite active inflammation of the glomeruli. There is considerable inflammatory proliferation and infiltration of the interstitial tissue. The epithelium shows only secondary changes and the arteries are normal.

CASE X

George O. Aged forty-three.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. More than ten months. Observed for two months.

Etiology. Unknown.

Course. He first noticed edema of the feet in November 1926. A physician saw him soon afterwards and found a marked proteinuria. He was first seen in April 1927 when there was a massive anasarca. The urinary sediment indicated an active inflammatory and degenerative renal lesion. There was some hypertension at first but during his stay in the hospital the blood pressure fell to within normal limits. He left the hospital on June 1, 1927, with some edema and without any evidence of change in the intensity of the renal lesion. He died early in September 1928, apparently of bronchopneumonia.

RELEVANT CLINICAL DETAILS

On November 1, 1926, when he was feeling perfectly well, he was surprised to find his ankles were swollen. He is sure that there was no illness of any sort during October, but some time in September he had had a bad cold and for some days had felt quite ill, though he had been able to continue his work. The edema increased very rapidly so that by November 9, when he visited a doctor, he was hardly able to get his clothes on. His physician found a large quantity of protein in his urine. The edema became still more extensive and during the next four months it was found necessary to remove large volumes of fluid from the abdominal cavity on several occasions.

He was admitted to the hospital on April 21, 1927, with an extreme edema of all the subcutaneous tissues, with fluid in both pleural cavities and with ascites. Over 8 liters of milky fluid were removed from the abdomen. This fluid contained only 0.08 gm. of protein per 100 c.c. The heart seemed to be enlarged to the left. The blood pressure was 180 systolic and 100 diastolic but it gradually fell and a week after admission was 130 systolic and 70 diastolic. There was no evidence of peripheral arteriosclerosis. The retinal vessels appeared to be normal. There was a slight degree of anemia. The Wassermann reaction was positive. The basal metabolism calculated for his ideal weight was −22 per cent. The blood urea concentration was 53 mg. per 100 c.c.

On April 22 a concentration test with a twelve hours' volume of 274 c.c. and a specific gravity of 1.019 was obtained. The rate of protein excretion was 2060 mg. per twelve hours. There was 5,300,000 casts, 1 per cent epithelial, 2 per cent granular, 4 per cent fatty, 1 per cent waxy and the remainder were hyaline casts, almost all of them with fat droplets and many with degenerated cells embedded within them. The number of red blood cells was 12,100,000 per twelve hours. The intensity of the degenerative process was shown by a twelve hours' rate of excretion of white blood and epithelial cells of 83,500,000. Among them were many "oval fat bodies."

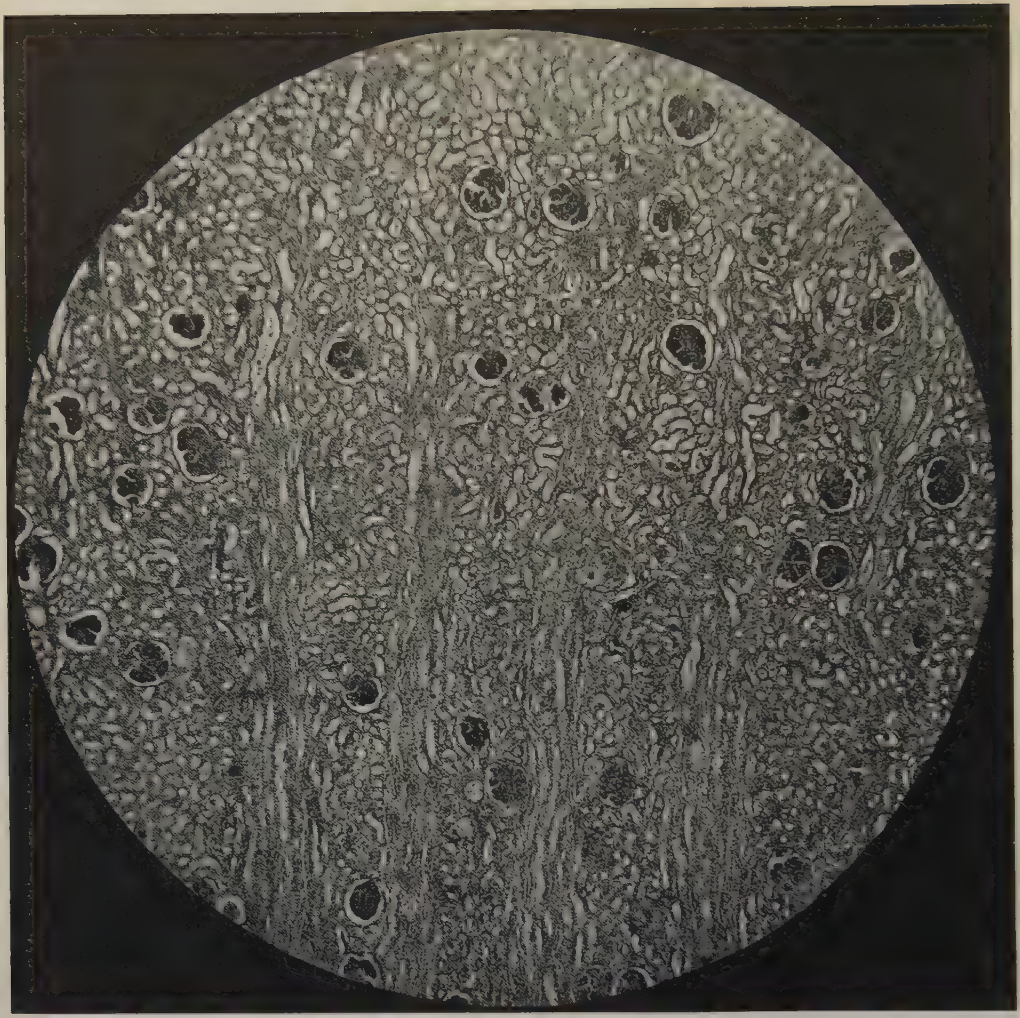

PLATE X A

The most striking feature is the tremendous enlargement of the glomeruli, a result of a typical intracapillary glomerulitis. The interstitial tissue shows only a slight proliferation though it is heavily infiltrated with inflammatory leucocytes. The arrangement of the tubules is still fairly normal.

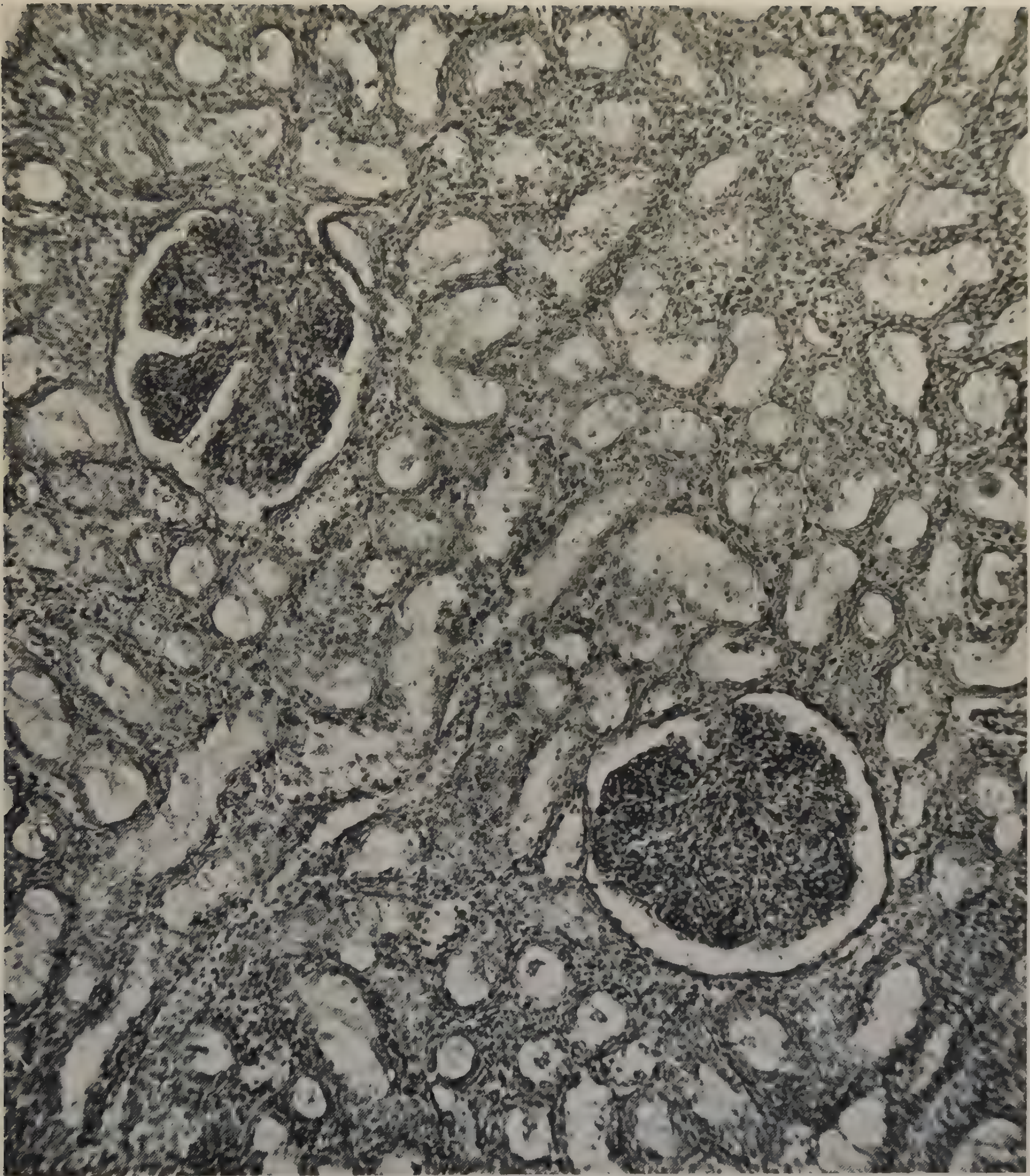

Plate X b

The tremendous enlargement of the glomeruli due to a cellular increase in the glomerular tuft is well seen. Throughout the interstitial tissue is a heavy leucocytic infiltration. The degeneration of the tubular epithelium is quite apparent. (Cf. Plate lxxxix.)

Efforts, not entirely successful, were made to induce the patient to take enough protein without salt, and there was a slow decrease in the edema. On May 14 another concentration test had a volume of 267 c.c. with a specific gravity of 1.020, and a twelve hours' protein excretion of 2910 mg. The number of casts was 2,970,000 with 8 per cent granular, 8 per cent fatty, and 84 per cent of hyaline casts studded with fat droplets. The number of red blood cells was 53,000,000 and of white blood cells and epithelial cells 56,000,000. This was taken as evidence of the continuance of a very active inflammatory and degenerative renal lesion.

The patient returned to his home in the country a few days afterwards, and was not heard from again until the news of his death came towards the end of September 1928. His physician stated that the cause of death was bronchopneumonia.

PATHOLOGICAL OBSERVATIONS

Postmortem examination was limited to a removal of the kidneys. They were slightly enlarged, measuring 13 × 7 × 4 cms. Their capsules stripped easily leaving a smooth surface of normal color. The cut surface showed no very definite abnormalities. The arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are greatly enlarged, some measuring twice the size of the average normal diameter, more than an eight fold increase in volume. The enlargement is due to a marked increase in the cells of the tuft, as this structure is heavily infiltrated with leucocytes, principally mononuclears but also with a moderate number of polymorphonuclears. There are also present many larger oval nuclei, evidently of endothelial cells, though since the capillaries are obliterated their exact relations are difficult to see. Fibrin thrombi or areas of necrosis in the tuft are rare. Bowman's space occasionally contains granular material, and there is present an occasional adhesion to the tuft, but no typical glomerular crescents of exudate and cells are present.

Tubules. The general appearance of the convoluted tubules in the cortex is well preserved. Their epithelium, however, shows varying degrees of cloudy swelling and there is granular material in the lumens of many of them. These degenerative changes are especially well marked in the deeper layers of the cortex. Casts are not numerous, a few hyaline and granular ones being present in the straight tubules.

Interstitial Tissue. There is a moderate diffuse increase in the amount of connective tissue in the interstitial framework of the cortex, and the tubules are separated by this proliferation. In the increased connective tissue is a very definite infiltration with leucocytes of both the mononuclear and polymorphonuclear type. The infiltration is diffuse with focal denser accumulations in small scar-like areas.

Arteries. The arteries are essentially normal. There is a slight increase in the connective tissue of the intima of some of them.

SUMMARY

The kidney shows a very typical intracapillary inflammatory involvement of the glomeruli of extreme degree and in a state of moderate activity. Inflammatory lesions are also present in the interstitial tissue. The tubules show slight degenerative changes and the arteries are normal.

CASE XI

Edward R. Aged fifty-three.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Two years? Observed during the last three months.

Etiology. No information.

Course. There is a history of what was probably the initial stage of a glomerular nephritis in the spring of 1923. This was followed by a latent period and the development of uremia in April 1925, before evidences of the terminal stage had appeared.

RELEVANT CLINICAL DETAILS

About March 1923 his face and legs became swollen. So far as he can remember there were no other symptoms. He went to a doctor who examined his urine and told him he had kidney trouble. He never before had had to go to bed on account of illness.

He apparently recovered rapidly and remained free from symptoms until February 1925, when the edema of his face and legs returned for about two weeks accompanied this time by a dull headache, weakness and loss of appetite. About the same time he began to cough though there was very little expectoration. He visited the hospital for a few days towards the end of February 1925. A concentration test showed a rate of protein excretion of 2590 mg. per twelve hours. There were 221,000 casts of which 2 per cent were epithelial, 2 per cent waxy and the remainder hyaline casts sprinkled with fat droplets. There were 172,000,000 red blood cells and 31,000,000 white blood cells and epithelial cells. Many of the epithelial cells contained fat. These findings suggested the existence of an active renal lesion inflammatory in origin but with a degenerative process superadded. The physical examination at this time gave evidence of a bronchopneumonia at the base of the left lung. There was a moderate anemia (3,200,000 red blood cells per cubic millimeter) and a slightly enlarged heart with a blood pressure of 165 systolic and 90 diastolic. He left the hospital against advice before anything more was ascertained.

During March he was in a hospital in Fort Bragg for a few days. There his blood pressure varied from 190 systolic and 115 diastolic to 210 and 130.

On April 3 he was brought back in a semicomatose state, with marked edema of the legs and ascites. The edema almost cleared up under digitalis but the blood urea concentration which had been 118 mg. per 100 c.c. on April 13 had risen to 503 mg. on April 24. On that day a concentration test with a volume of 265 per twelve hours and a specific gravity of 1.013 was collected. The number of red blood cells was 784,000,000 and there were 95,000,000 white blood cells and epithelial cells per twelve hours. The number of casts was 8,800,000 of which 2 per cent were blood casts, 18 per cent epithelial, 16 per cent granular, 20 per cent hyaline, while 44 per cent were of the renal failure type. The patient was then comatose. Signs of pericarditis had developed. He died that night.

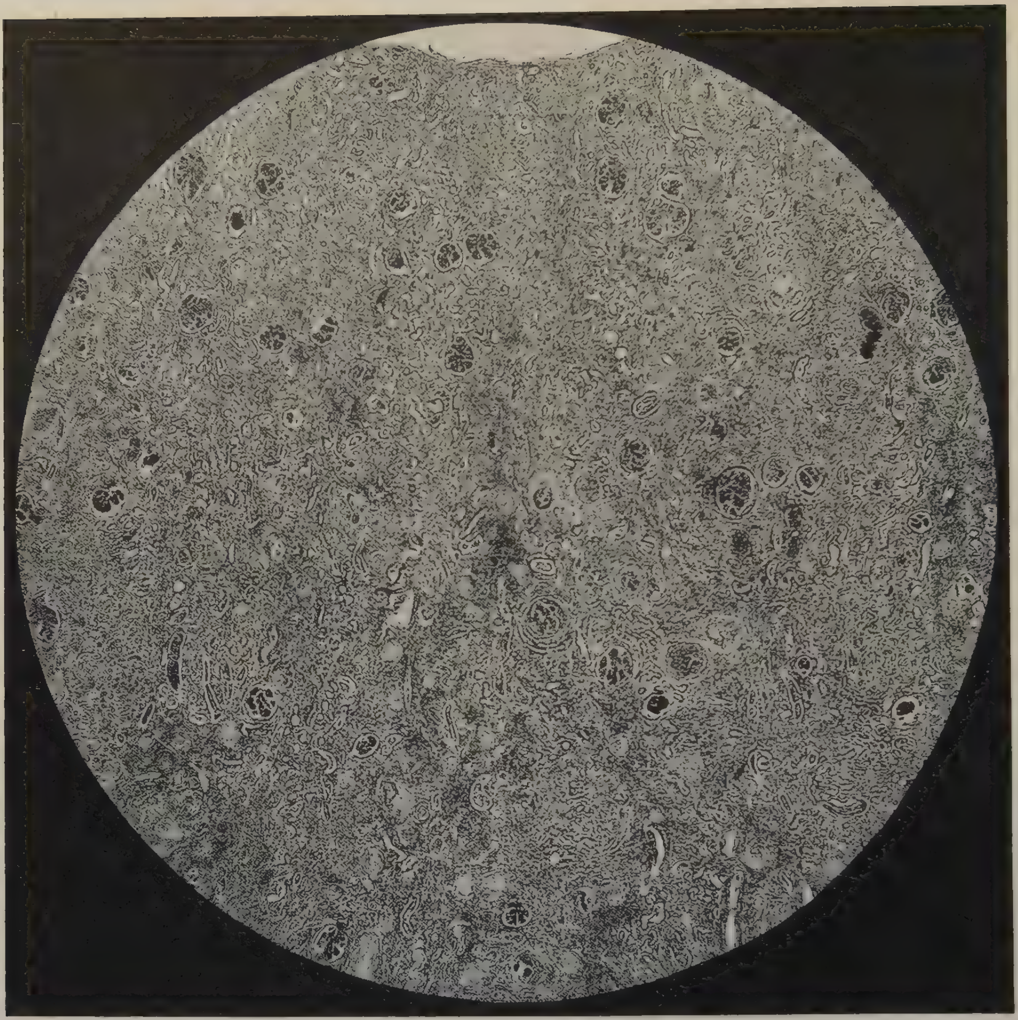

Plate XI a

There is a diffuse and even proliferation of the connective tissue of the kidney with scattered areas of leucocytic infiltration. As a result there is widespread tubular atrophy. The glomeruli are either enlarged or shrunken as a result of the inflammation in them.

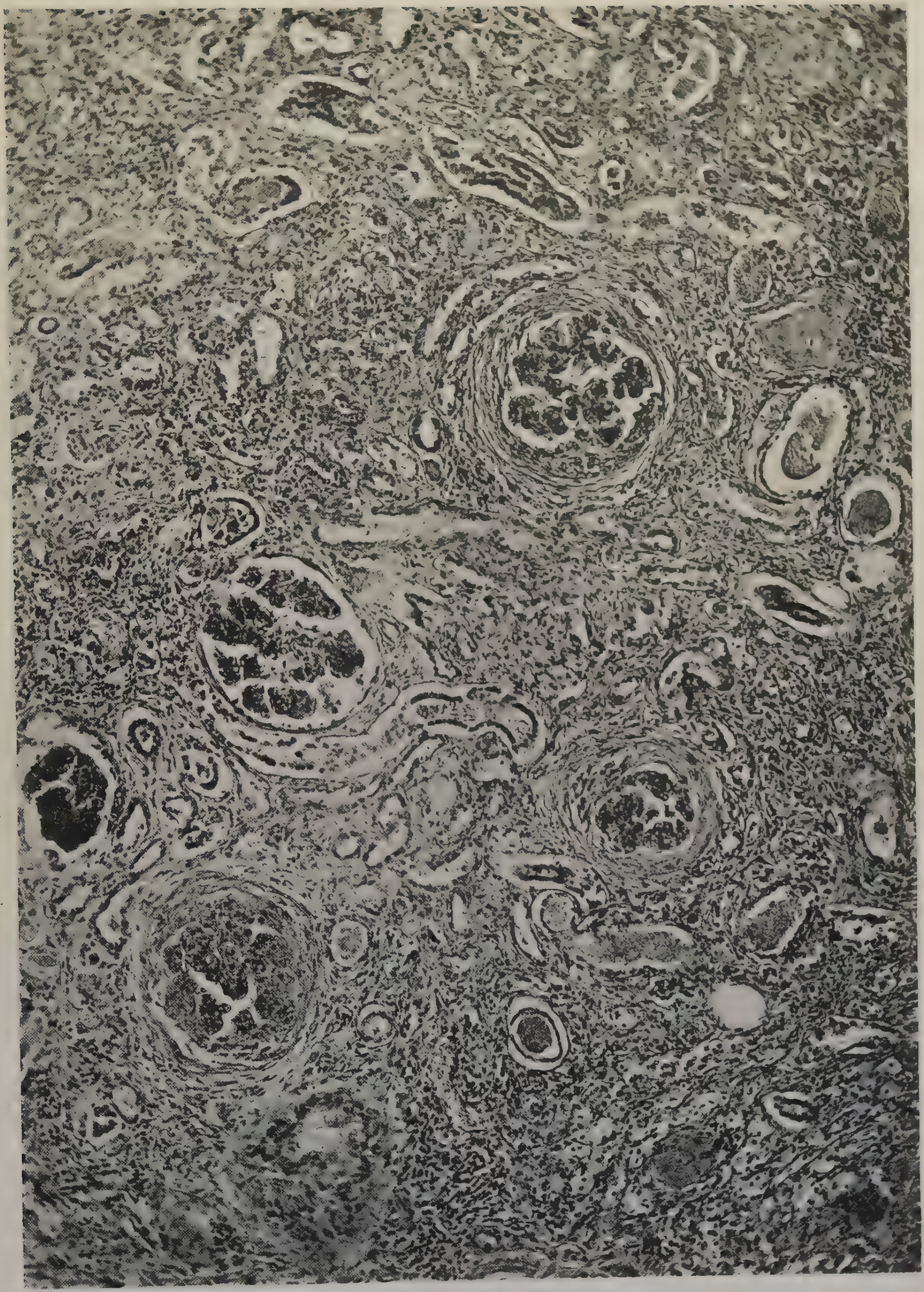

PLATE XI B

All of the glomeruli show the inflammatory process. In some there is considerable connective tissue formation. There is marked cellular infiltration and proliferation of the interstitial tissue with consequent deformity of the tubules. Many casts of all sorts in the latter.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a terminal bronchopneumonia with an acute fibrinous pleurisy and fibrinous pericarditis. There was also a secondary anemia with pigmentation of the spleen, a healed apical tuberculosis and a generalized arteriosclerosis of moderate degree.

The kidneys were of normal size, measuring 12 × 5 × 4 cm. There were some adhesions between the capsule and cortex, and the surface of the kidney was definitely granular. Many petechial hemorrhages were present. The cut surface showed indefinite markings and was congested. The arteries showed a slight thickening and rigidity of their walls.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus is involved in varying stages of the inflammatory process. In some the lesion is of the extracapillary type with infiltration with leucocytes and partial fibrosis of the tuft and there are partially organized crescents in Bowman's space. In others, about one-half those studied, the lesion is more intracapillary and consists of a heavy infiltration of the tuft with leucocytes. Polymorphonuclears are present in considerable numbers, the tuft is swollen, but their is little development of fibrous connective tissue. Scattered among these two types of lesions and comprising about one-fourth the total number of glomeruli, are hyaline masses, some of which can still be recognized as fibrosed tufts.

Tubules. There is considerable deformation of the architecture of the cortex from the developing connective tissue and round cell infiltration of the interstitial tissue. In some places the general shape of the tubules and of their lining epithelium is well preserved. but through the greater part of the section they are collapsed and compressed and their epithelium is atrophic and distorted in shape. Many of the tubules are lined with irregularly shaped cells with large oval hyperchromatic nuclei which are evidently a regenerated lining for the tubule lumen. Active degenerative processes, such as cloudy swelling and necrosis are only occasionally found. The lumens of the tubules contain casts of all sorts, and red blood cells, some evidently recently shed and others amalgamated into definite blood casts. There are also many polymorphonuclear leucocytes both in the casts and free in the lumens of the tubules.

Interstitial Tissue. There is a wide spread diffuse proliferation of connective tissue throughout the cortex in the interstitial framework and an accompanying round cell infiltration. Scar-like depressions, especially heavily infiltrated with both lymphocytes and polymorphonuclear leucocytes, are scattered beneath the cortex.

Arteries. There is a moderate fibrous proliferation of the connective tissue of the intima of the arcuate arteries and the smaller branches to the cortex are more prominent than normal due to a similar fibrous thickening of their walls.

SUMMARY

The glomeruli show old and recent intracapillary and extracapillary inflammatory lesions. The interstitial tissue is actively proliferating and the presence of polymorphonuclear leucocytes both in the tufts and in the lumens of the tubules, as well as red blood cells, is evidence of the activity of these inflammatory processes. The arteries show a moderate sclerosis.

CASE XII

James R. Aged twenty-five.

Clinical Diagnosis. Hemorrhagic Brights disease, active stage.

Duration. One hundred and fifty-four days. Observed for last seventeen days.

Etiology. No information.

Course. In October 1918 he passed through the initial stage but apparently without any pronounced symptoms. A few months later anasarca, retinitis and pulmonary edema developed. When he was seen in March 1919 he was too ill to give any detailed history. At that time the urinary sediment was typical of the active stage of the disease except that a certain percentage of the casts were of the renal failure type. He developed pericarditis and died sixteen days after admission. The blood urea concentration was 186 mg. on the day of death.

RELEVANT CLINICAL DETAILS

On October 17, 1918, while serving with the army in France he reported sick and was told that there was something wrong with his kidneys. He had no clear recollection of his symptoms at that time but he remembered that a great many examinations of the urine were made. There was no history of any preceding infection. Unfortunately no records were sent with him, and he was not seen until he was so ill that he could not be questioned thoroughly. Apparently very obvious symptoms did not develop for some months, but on the voyage home his legs and arms became swollen, and his vision was blurred. While he was on the train travelling to Camp Lewis, Washington, he became very short of breath and had much cough and expectoration. On his arrival on March 5, 1919, there were signs of pulmonary edema and the sputum was foamy and blood tinged. The blood pressure was 175 systolic and 115 diastolic. The heart was enlarged. There were exudative plaques and many hemorrhages in the retinae. Definite edema was present only in the face. The blood urea concentration was 75 mg. per 100 c.c. The urine was cloudy with casts and cells and microscopically large numbers of lyzed red blood cells were found. The number of casts was very considerable. Among them were many epithelial, granular, waxy and fatty casts and there were also some typical renal failure casts.

The patient held his own for a week, but thereafter the systolic pressure began to fall, the heart grew larger and signs of pericarditis developed. He died on the seventeenth day after admission but of circulatory failure rather than of uremia, for the blood urea concentration was only 186 mg. per 100 c.c. on the day of his death.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained after death. They were of normal size and their capsules stripped with some difficulty leaving a finely granular greyish-red surface.

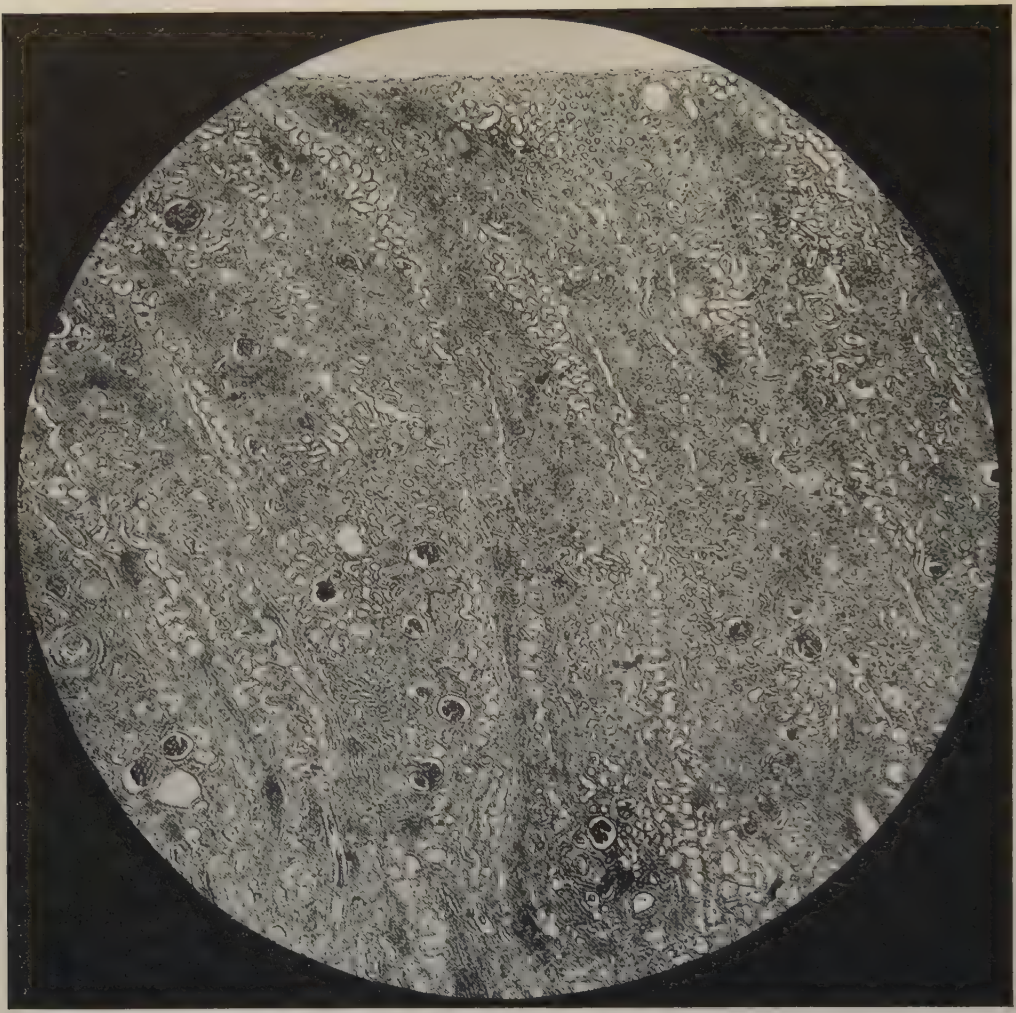

Plate XII a

There is a very marked alteration of the structure of the cortex as a result of the irregular proliferation of the interstitial tissue of the kidney framework. Most of the glomeruli are destroyed, and there is widespread atrophy of the tubules. Considerable round cell infiltration is scattered irregularly throughout the section.

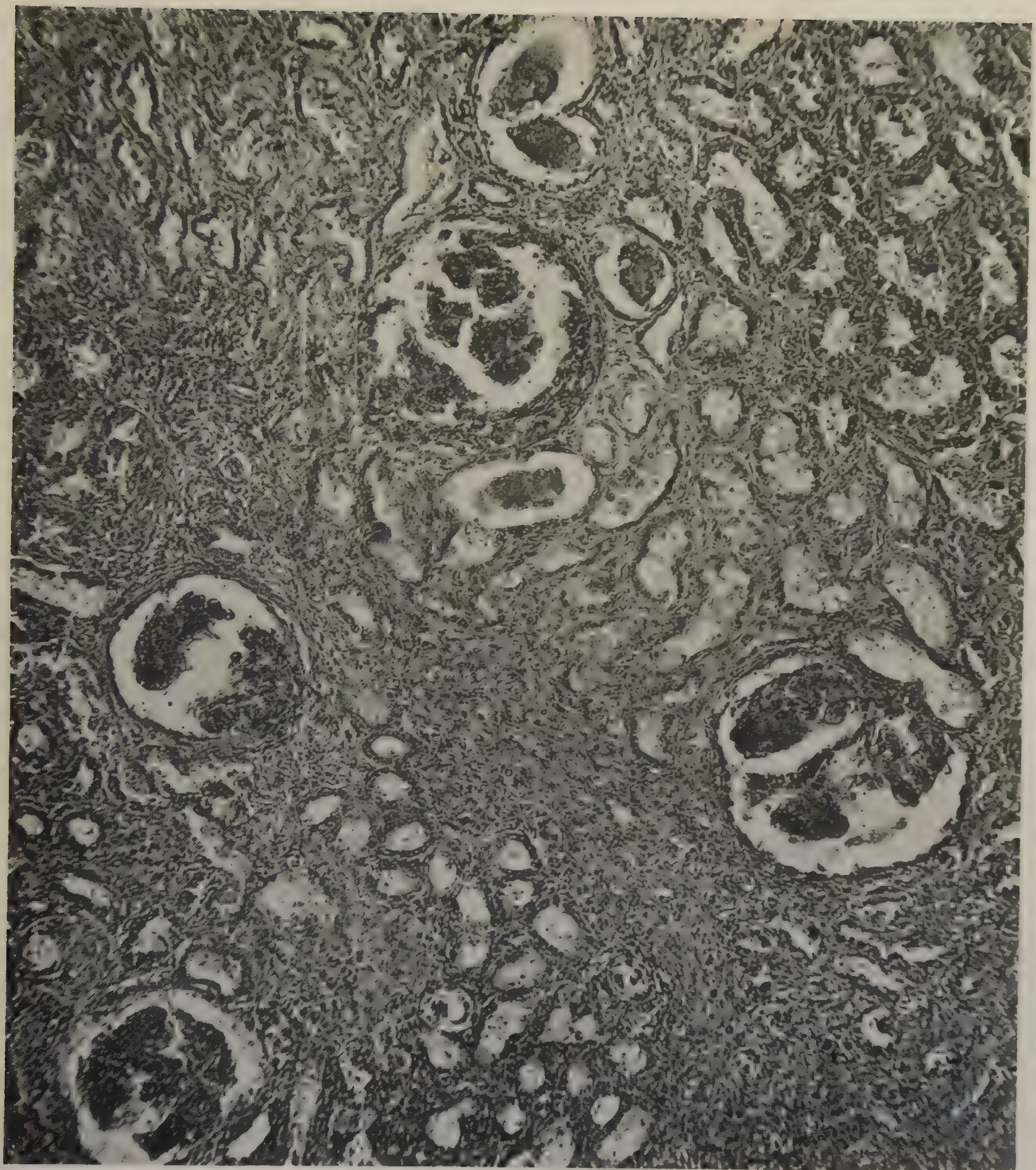

Plate XII b

There is a very heavy round cell infiltration of the interstitial tissue with development of connective tissue in other places. The distorted tubules are lined with atypical epithelium. In the glomeruli are seen the usual inflammatory processes.

No gross petechiae could be seen. The cut surface showed some scarring and indistinct markings. The pelvis and renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli show inflammatory lesions. In the majority the process consists of an infiltration of the tuft with leucocytes associated with a development of fibrous connective tissue which obliterates capillaries and forms adhesions to the parietal layer of Bowman's space. The latter frequently contains exudate and in rare instances definite glomerular crescents are found. Very occasionally one finds a glomerulus which is almost entirely fibrous. Such hyaline masses are usually located in a place where the connective tissue proliferation of the interstitial tissue has formed a scar-like area.

Tubules. The tubules of the cortex are markedly deformed by the proliferation of the interstitial tissue. In large areas they are collapsed and compressed and their epithelium is atrophic. In other places, they are dilated to form cyst-like spaces which contain hyaline material. In other regions, the tubules have essentially their normal structure, except that they are one and one-half times their normal diameter and their epithelium is correspondingly thick. Degenerations, such as cloudy swelling, are present in the convoluted and straight tubules. Their lumens contain casts of various sorts, including an occasional blood cast and many large renal failure casts in the large collecting ducts.

Interstitial Tissue. There is a marked proliferation of the interstitial tissue. Throughout large areas the tubules and glomeruli are almost replaced by scar tissue, and when this reaches the free surface of the kidney a depression is formed. The new formed connective tissue is still rather cellular and is diffusely infiltrated with leucocytes, many of which are of the polymorphonuclear type.

Arteries. The arteries show no significant lesions.

SUMMARY

The kidneys show a well-developed active glomerulitis, with connective tissue formation beginning in the tufts and extensively developed in the interstitial tissue. The tubules are distorted by this fibrosis, but show only mild degenerative lesions. Renal failure casts are present in large numbers in the tubular lumens as are leucocytes and red blood cells. The arteries are essentially normal.

CASE XIII

Adolph S. Aged twenty-nine.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. One month.

Etiology. Streptococcus, hemolytic.

Course. Initial stage was typical with hematuria and edema. This was followed by fever, and a rapidly progressing anemia. Blood culture showed a pure culture of a hemolytic streptococcus. There was evidence of aortic regurgitation and of mitral stenosis. Three weeks after the onset the blood urea concentration was 209 mg. per 100 c.c. The urinary sediment was typical of the initial stages of a hemorrhagic Bright's disease with the exception that 27 per cent of the casts were of the renal failure type. A week later the patient suddenly died.

RELEVANT CLINICAL DETAILS

Four weeks before he died the patient found that his ankles were swollen and on the same day he observed that his urine had a dark brown color. He consulted a doctor who told him he had inflammation of the kidneys. There had been no preceding tonsillitis or obvious infection but he had felt tired and weak for several weeks. With rest in bed the edema decreased but the urine was still bloody.

On admission to the hospital a week before his death he was found to have a fever which at times rose as high as 102°F. There were several hemorrhagic spots on the skin. The red blood cells numbered 2,600,000 per cubic millimeter and the white blood cells were 15,000 with 82 per cent of polymorphonuclear leucocytes. A pure culture of a hemolytic streptococcus was obtained from the blood. The heart was enlarged and a diastolic murmur was heard along the sternum and a presystolic murmur at the apex. The systolic pressure was 118 and the diastolic about 50, although some sound could be heard to zero. The blood urea concentration was 206 mg. per 100 c.c.

The concentration test urine had a volume of 760 c.c. for twelve hours and a specific gravity of 1.014. The rate of protein excretion was 220 mg. per twelve hour period. The urine was not obviously bloody but it contained 24,000,000 red blood cells and 62,000,000 white blood cells and epithelial cells. In twelve hours 2,300,000 casts were excreted. The differential count was as follows:

Casts	*Per Cent*
Blood	12
Epithelial	15
Granular	18
Waxy	3
Hyaline	25
Renal failure	27

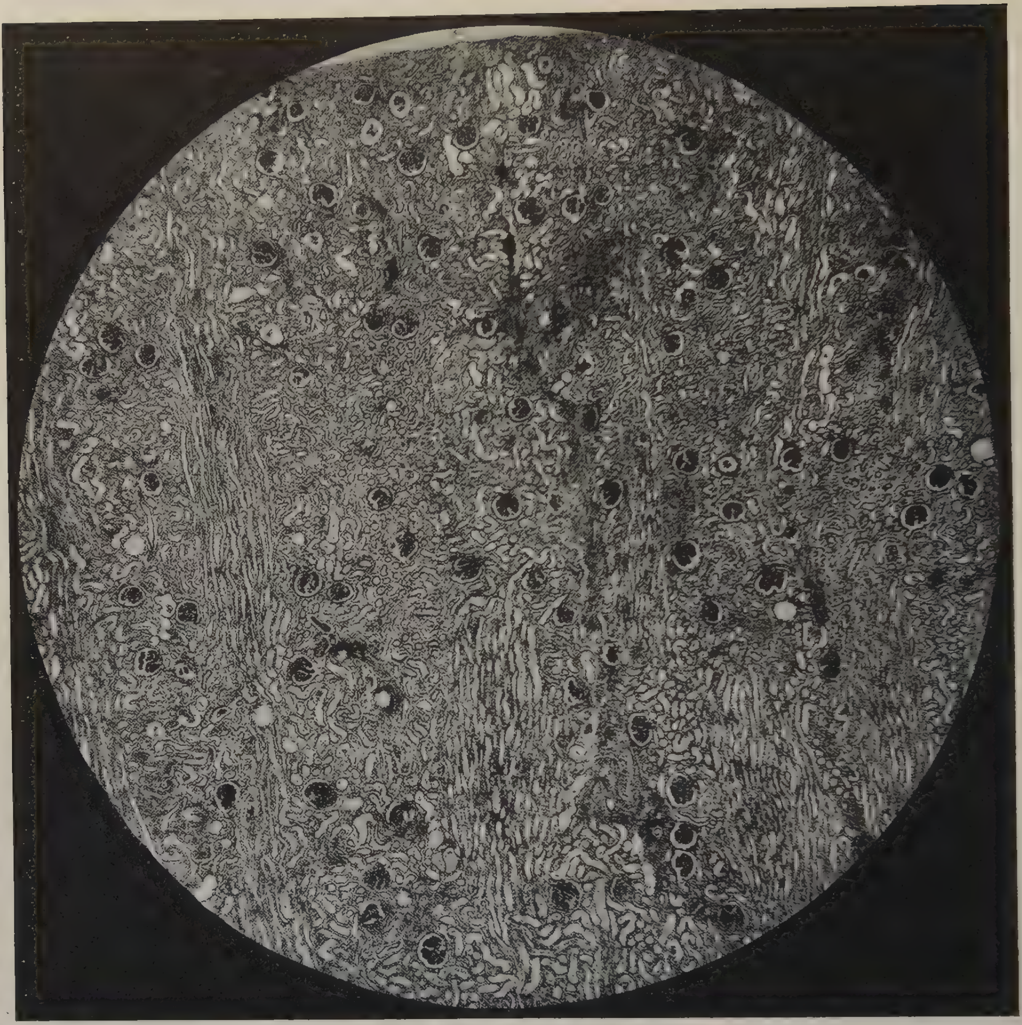

Plate XIII a

The numerous glomeruli appear as dark spots from the heavy leucocytic and fibrotic changes occurring in them. There is a slight diffuse thickening of the interstitial tissue with irregular dark areas of leucocytic infiltration. The general structure of the tubules is still fairly well preserved.

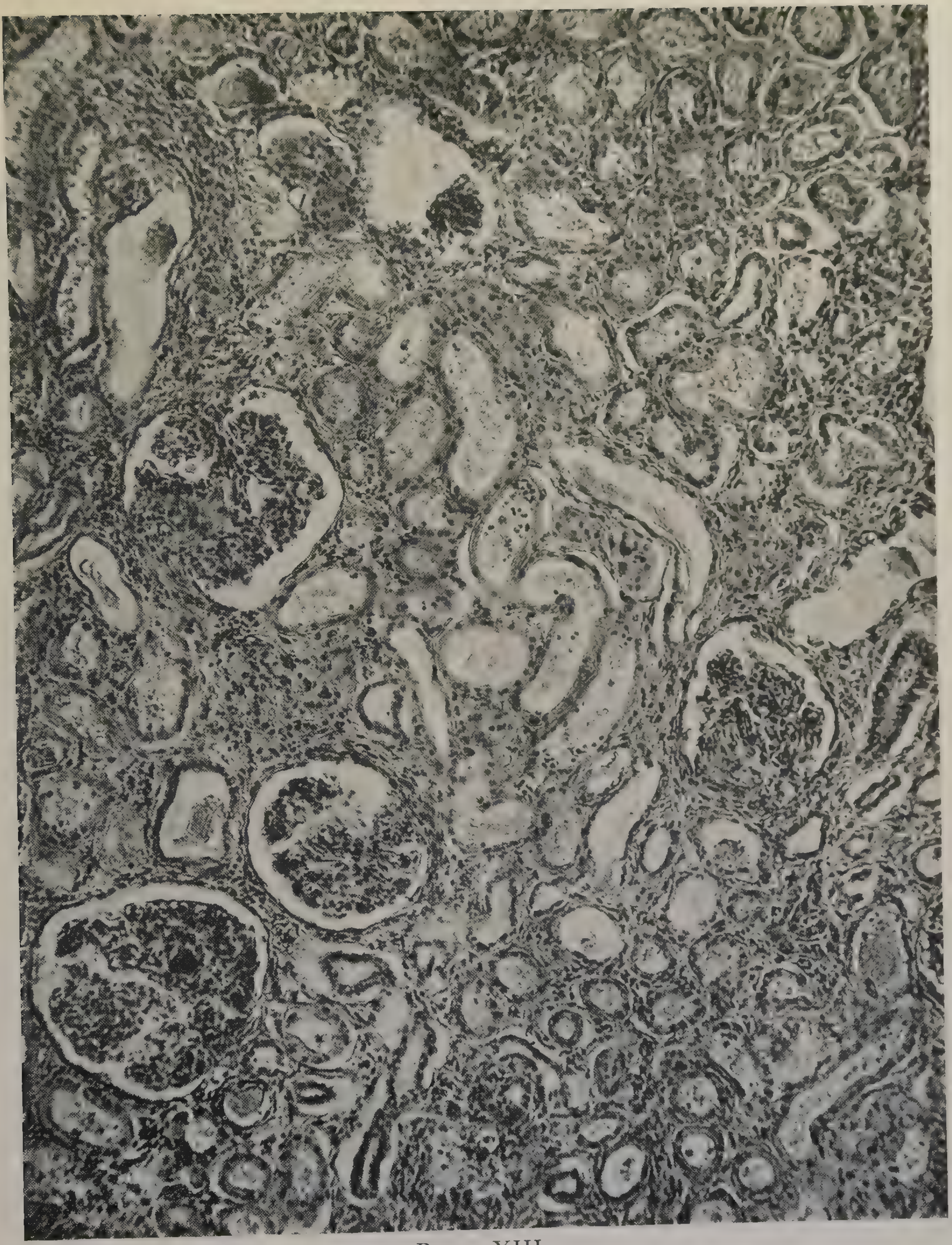

PLATE XIII B

The inflammation in the glomeruli is chiefly of the intracapillary type, and connective tissue formation may be noted in some of the tufts with capsular adhesions in others. There is an early cellular inflammatory reaction in the interstitial tissue. Granular debris and leucocytes are seen in the tubules. (Cf. Fig. 18, Plate LXXXVIII.)

There was evidence therefore of an active hemorrhagic Bright's disease with pronounced cellular desquamation but no indications of fatty degeneration. Seven days after this examination the patient died.

PATHOLOGICAL OBSERVATIONS

There was found at autopsy a subacute ulcerative endocarditis with severe involvement of the aortic and mitral valves. There was a marked edema of the feet and legs and collections of fluids in all the serous cavities. Smears of the thrombotic masses on the heart valves showed long chains of gram-positive diplococci.

Both kidneys were swollen, measuring 14.5 × 7.5 × 4 cm. The capsule was edematous and stripped easily leaving a smooth surface of light brown color in which were small hemorrhages. On the cut surface the cortex was wide and opaque. The arteries were apparently normal. The right kidney was the same as the left.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all of the glomeruli show an active glomerulitis of the intracapillary type. The tufts are swollen and infiltrated with leucocytes, many of which are of the polymorphonuclear type. Hyaline thrombi are also seen in the capillaries of the tufts and occasionally small areas of necrosis. (Cf. Fig. 18.) Adhesions between the tufts and the capsule are present but there are no collections of exudate in Bowman's space.

Epithelium. The epithelium of the convoluted tubules and ascending tubes of Henle's loop shows a moderate cloudy swelling and not infrequently necrosis and desquamation is found. The convoluted tubules in isolated groups contain coagulated material and freshly shed red blood cells. In the collecting tubules are many well-organized casts of all types, hyaline, granular and blood casts.

Interstitial Tissues. There is a definite edema of the interstitial tissue with separation of the connective tissue reticulum by fluid. There is also a diffuse infiltration with leucocytes, including polymorphonuclears, and in areas a definite but moderate production of new fibrous connective tissue. There is however little if any deformity of tubules by this proliferation.

Arteries. The arteries are esentially normal.

SUMMARY

The kidneys show a recent active glomerulitis of the intracapillary type with evidences of capillary embolism and moderate epithelial degeneration.

Case xiv

Jane S. Aged eight.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. One year?

Etiology. Unknown.

Course. The condition was first discovered through the development of a soft pitting edema accompanied by an intense proteinuria six months before her death. When first seen three weeks later the urine showed all the signs of hemorrhagic nephritis in the active stage. There was no change until three days before the end when she became apathetic, complained of headache, lost her vision, and had a series of convulsions which lasted for several hours. There was retinal edema and a high diastolic pressure. She never recovered consciousness and seemed to die of cerebral edema rather than of uremia.

RELEVANT CLINICAL DETAILS

The exact date at which this lesion began is unknown. In October the left femur was broken in an automobile accident. Attempts at reduction failing the bones were connected by plating in December. At that time and throughout the next month several routine urine examinations revealed no abnormality. In March of the following year shortly after the cast had been removed and when she was getting about on crutches a marked edema of both ankles was observed and a distinct puffiness of the face. She felt quite well at the time. There had been no infection of any sort for several months. The edema was of the soft pitting type. There was no gross hematuria. She was taken to a doctor who found an unusually high concentration of protein in the urine.

She was first seen three weeks later. There was still a moderate degree of soft edema. The blood pressure was 135 systolic and 80 diastolic. There was no evidence of cardiac enlargement. The retinal arteries seemed to be narrower than usual. A concentration test gave a volume of 384 c.c. per twelve hours with a specific gravity of 1.019. There were 4200 mg. of protein. The number of casts was 1,050,000. The differential count gave 2 per cent epithelial, 6 per cent granular, 6 per cent fatty 6 per cent waxy and 80 per cent hyaline. All of these were covered with fine fat droplets. The urine was cloudy with cells. It was estimated that there were as many as 100,000,000 white blood and epithelial cells, and several million of these were the large cells with granules and fat droplets which we have called "oval fat bodies." But along with all this evidence of an intense degenerative lesion there were also very many faded red blood cells. The number was 170,000,000 per twelve hours.

The nature of the urinary sediment was thus quite typical of the active stage of a hemorrhagic nephritis. It was quite definitely not characteristic of the initial stage. The edema also was obviously not of the type found at the beginning of a hemorrhagic lesion. But if that is so we are obliged to suppose that the initial stage had escaped notice, and that is a supposition which is hard to make since the child had been under close medical observation during the preceding three months and only about a month before the appearance of the edema a routine urine examination had shown no abnormality.

The edema lessened and at last disappeared when the child took a low salt diet with a more than adequate protein content. The blood urea concentration was only 24 mg. per 100 c.c., and the blood pressure fell to 110 systolic and 80 diastolic during April.

She was seen on one day in June. There was no edema and she was in excellent spirits. But the blood pressure had risen to 135 systolic and 110 diastolic. The urine was too dilute to make counts reliable, but there was still at least 23,000,000 red blood cells and 31,000,000 white blood and epithelial cells, including 3,600,000 "oval fat bodies." The rate of protein excretion was 5070 mg. per twelve hours. The volume was 215 c.c. and the specific gravity 1.019.

On July 26 she was brought to the hospital in a deeply unconscious state. Two days before, after a period of apathy and lassitude, she had complained of a severe headache and had vomited. Shortly afterwards she said she could not see. An hour or so later she had a convulsion. Consciousness was recovered for an hour during which she had great pain in her head, and then a series of convulsions occurred which lasted at intervals for five and a half hours. She never thereafter became conscious.

On admission the blood pressure was 220 systolic and 120 diastolic, with a pulse rate of 120. There were no retinal hemorrhages or exudate but there was retinal edema. The blood urea concentration was 160 mg. per 100 c.c. No urine was obtained until two days later, shortly before death. The time interval over which the 53 c.c. collected by catheter were secreted was ten hours which is equivalent to a twelve hour volume of 64 c.c. The specific gravity was 1.023. There were 2768 mg. of protein. Of the 23,000 casts 24 per cent were renal failure casts, 50 per cent granular, 10 per cent waxy and 16 per cent hyaline. On the day before death signs of consolidation at the upper lobe of the left lung developed.

This was not uremia, nor had the lesion reached its terminal stage. Neither the beginning nor the end of its natural evolution was seen. Death was due to cerebral edema and to pneumonia.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were removed at autopsy. They were about normal in size, measuring 9.5 × 6 × 3.5 cm. The capsules stripped easily, leaving a fairly smooth greyish-pink surface on which might be seen a few scattered petechial hemorrhages. The cut surface showed a definite widening of the cortex. The renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are affected by the earlier stages of an acute glomerulitis. Most of them are greatly swollen. Their tufts are infiltrated with leucocytes and in some there are small patches of beginning fibrosis. These inflammatory lesions in many instances have spread into Bowman's space so that here are found fibrous adhesions and in other places glomerular crescents.

Tubules. The tubules in the greater part of the cortex have preserved their normal shape and arrangement. In the areas of scarring, however, they are collapsed, atrophied and distorted by the proliferating connective tissue. In many of the epithelial cells of both the normal and atrophic tubules there are evidences of degeneration such as cloudy swelling and even necrosis and desquamation. Some of the narrow irregular tubules are lined with regenerated immature epithelial cells. Casts of all sorts are present in the convoluted tubules in moderate numbers. Occasionally a moderate number of red blood cells can be found. In an occasional collecting tubule a broad renal cast is seen.

Interstitial Tissue. Throughout the cortex there is a diffuse rather early proliferation of the connective tissue. This tissue is still cellular and among the nuclei of the fibroblasts may be found inflammatory leucocytes, chiefly of the mononuclear type but also some of the polymorphonuclear type. This inflammatory tissue separates the tubules and causes the atrophy previously described.

Arteries. Both the larger arcuate arteries and their interlobular branches into the cortex show no significant lesions.

SUMMARY

The kidneys show early inflammatory lesions in the glomeruli and in the interstitial tissue. There are moderate degenerative changes in the epithelium of the tubules and the arteries are normal.

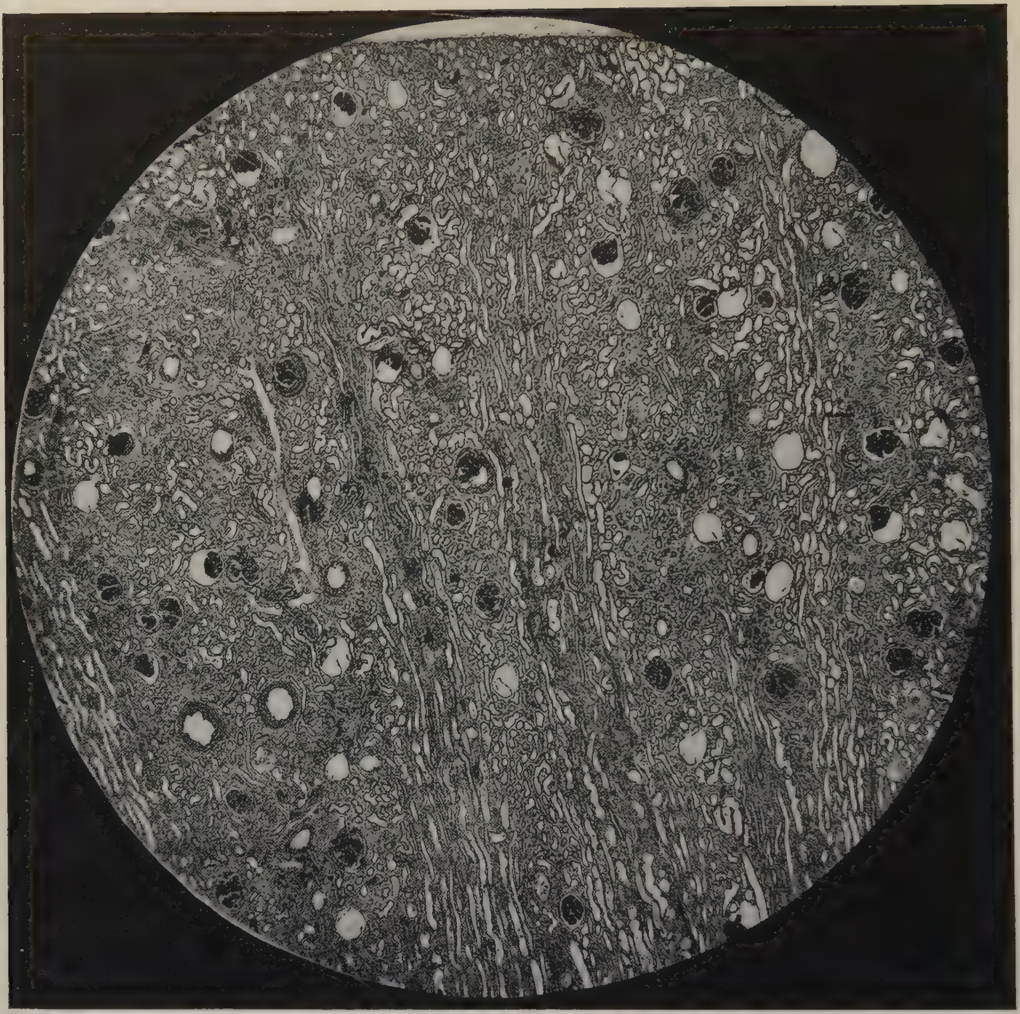

PLATE XIV A

All of the glomeruli stand out plainly as a result of the inflammatory processes in them. Many glomerular crescents may be seen. There is a beginning diffuse inflammatory proliferation of the interstitial tissue.

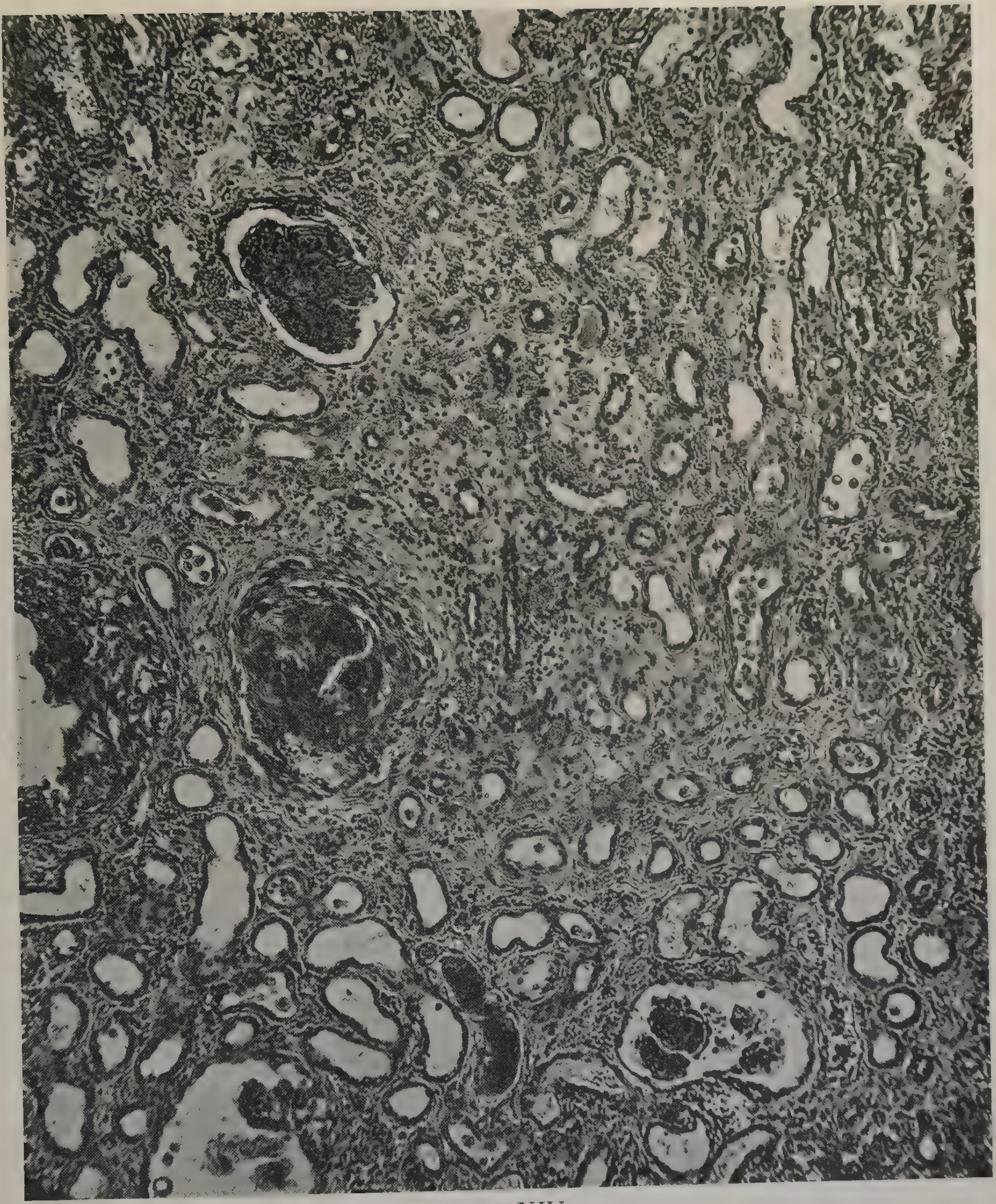

Plate XIV b

Several glomeruli with inflammatory crescent formation are seen. There is a marked proliferation of the interstitial tissue with diffuse leucocytic infiltration and tubular collapse and atrophy.

CASE XV

Robert T.

Clinical Diagnosis. Hemorrhagic Bright's disease, active stage.

Duration. Eleven years. Observed during the last six years.

Etiology. Streptococcal tonsillitis.

Course. The initial stage passed without pronounced symptoms and was followed by a latent stage which lasted for seven years broken only by three transient periods of activity resulting from infections. There was then a gradual transition to an active stage which continued until death. The terminal stage though approached was never fully developed.

RELEVANT CLINICAL DETAILS

This patient was a physician and gave a somewhat more accurately documented history than is usually obtainable. In 1913 he developed a severe tonsillitis. A few days later while he was still ill his wife and children became infected. Twenty-four hours after the onset a macular rash appeared on the children's skin, but he did not think that it resembled the rash of scarlet fever at all closely, although it was followed by desquamation. He had cultures made from throat swabs, and an almost pure culture of streptococcus viridans was reported. He was so busy looking after his family that he neglected to examine his urine. He noted no edema. He was easily tired and weak for several weeks afterwards and a month later had a partial paralysis of the muscles of deglutition which troubled him for some time. Even seven months later he was not so strong as before the tonsillitis and he then began to suffer from pain and slight swelling in both knees and both feet. Later one elbow joint and both thumbs became involved. After a week of this he consulted a medical friend who put him in a hospital. There it was discovered that there was a considerable amount of albumin in the urine. He got no other details of the urinary findings but he remembers that his friend looked sceptical when he said that he had never had nephritis. After several partial recoveries from the arthritis he was able to resume practice after four months' illness, though he still felt weak and incapacitated.

During the next six months he occasionally examined chance specimens of urine and usually found a little albumin and sometimes hyaline casts. He is sure that there was never any gross hematuria. His mind was at last delivered from fear of Bright's disease when a physician was unable to discover any albumin in the night urine although it was present during the day. Since his "phthalein" excretion and blood pressure were within normal limits a diagnosis of orthostatic albuminuria was made.

During the winter of 1914 he had several prolonged respiratory infections, and was troubled a great deal by a diarrhea which he at last found could be controlled by hydrochloric acid. A medical consultant who examined him at this time told him that he had nephritis, myocarditis and colitis and said he never would be able to practice again. However he went back to work and found that his health was improving. In 1915, happening to be in Chicago, he was thoroughly examined in a University Hospital. The renal condition was pronounced to be trifling but he was advised to have his tonsils removed. After their enucleation the bacteriological laboratory reported that they were extensively diseased and obtained a pure growth of a streptococcus on culture.

Thereafter he felt much stronger and continued active practice. But in the summer of 1916 after a long swim during which he became very cool he had a chill and a slight fever for a day. A week or so later he sent a specimen of his urine to a laboratory and was told that it contained a considerable amount of blood and a number of hyaline and granular casts. Within two weeks however several entirely negative urine reports were obtained.

In 1917 he applied for service in the army but was at first rejected because albumin was found in the urine. He gave his history and when a second specimen of urine was found to contain no albumin he was granted a commission in the Medical Corps. He was ordered to accompany a troop train from the west coast to New York. On the way there was an outbreak of tonsillitis and when he arrived at New York he had a fever and felt very ill. He nevertheless took a train bound for Camp Lewis, Washington, but when he reached Chicago was too sick to go on and entered the Presbyterian Hospital under the care of Dr. R. D. Woodyatt, who informed him that his throat and bronchial infection was not of much moment but that his renal condition was serious since there was definite evidence of acute nephritis. After two weeks in bed he continued his journey although the urine was still smoky with blood. However when he reached Camp Lewis the official examiner was unable to find anything wrong and sent him to full duty.

The first opportunity to make at least a partial examination came in 1918 at Camp Lewis. He was then in fairly good health, but the concentrated night urine obtained after abstention from fluids during the day contained a small amount of albumin and in the sediment a few blood casts and many red blood cells were always found. Several phenolsulphonephthalein tests gave normal results and his blood pressure was always low or near the normal average. There was no evidence of cardiac enlargement but extrasystoles were not infrequent.

From the quite typical urinary findings and from the history it was concluded that he was in the latent stage of a hemorrhagic Bright's disease.

During the latter part of 1918 the albuminuria became somewhat more marked and in 1919 when he was examined at the time of his discharge from the army it was sufficiently pronounced to lead to a diagnosis of "chronic nephritis."

In July 1920 the first ratio test was carried through. The result showed that 91 per cent of his renal tissue was still functioning. The blood urea concentration was 23 mg. per 100 c.c. There was not much albumin in the urine but there were an abnormal number of red blood cells. There were only a few casts of which about 30 per cent were blood casts. The hyaline casts contained no fat droplets. At this time then he was still in the latent stage and there was no serious reduction in the amount of renal tissue and no evidence of any actively degenerative renal process.

In the spring of 1921 the rate of protein excretion became very large and there was a sharp fall in the gradually decreasing amount of functioning renal tissue. Some of the main features of the progress during this active stage have been charted in Figure 20.

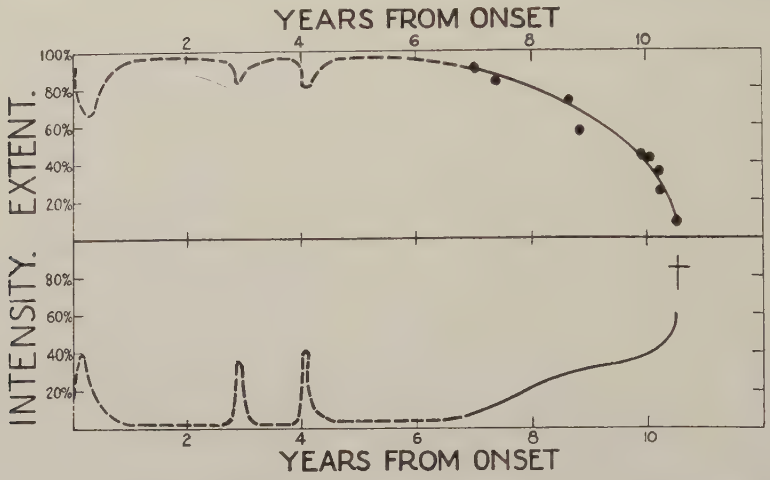

FIG. 20. Upper curve represents changes in amount of functioning renal tissue. Dots are actual determinations. Lower curve represents general change in intensity of pathological process as judged by sediment counts. In both curves broken lines are hypothetical and indicate nature of changes which may have occurred during exacerbations.

The nature of the changes which were occurring in the kidney are also apparent from a consideration of the differential cast counts made during the next three years. These are given in Table XXII.

Up to the very end the patient continued his medical work though it was of a relatively easy nature. The blood pressure remained within normal limits until 1923 when the systolic pressure varied from 140 to 190 and the diastolic from 100 to 130. These were increasingly frequent extrasystoles and some dyspnea on exertion. In 1923 headache, nausea and gastrointestinal disturbances of various types became increasingly more frequent. On Christmas day 1923 he drove his family 130 miles into the country but was then seized with severe abdominal pains and profuse diarrhea and vomiting. When seen next day in the country he was unconscious and the systolic pressure was only 65. After salt solution given intravenously he recovered consciousness and next day some urine was voided. The blood urea concentration at that time was 108 mg. per 100 c.c. Thereafter complete anuria set in and lasted until his death on January 2, 1924. Although no examinations had been made since September 1923 it was thought that he was still at the commencement of the terminal stage and might have lived longer if the dehydration had not led to a marked loss of function of the remaining fraction of renal tissue.

TABLE XXIV

Date	Number of casts in 12 hrs.	Differential						Renal failure, per cent	R.B.C. 12 hrs.	W. & Ep. 12 hrs.	Prot. mgm. 12 hrs.	Vol. sp. gr.	Blood urea	Renal tissue per cent of normal
		BL., per cent	EP., per cent	GR., per cent	FA., per cent	W., per cent	HY., per cent							
1920 July	....	35	35	15	0	0	15	0	....	....	.....	....	23	91
Nov	....	9	7	12	3	0	69	0	....	....	720	270 1.029	...	85
1921 Feb	....	8	0	32	0	0	60	0	....	....	.....	.....	29	
1922 Feb	4,540	1	4	4	4	1	86	0	....	....	1,760	407 1.026	...	86
July	....	0	8	0	10	0	82	0	....	....	4,050	295 1.032		
Dec	990,000	2	8	8	10	0	72	0	....	....	5,380	565 1.026	...	59
1923 April	1,080,000	2	2	1	17	1	73	4	3,740,000	888,000	3,500	534 1.026	...	46
June	....	0	9	4	12	10	62	3						
Sept	4,075,000	0	2	0	2	1	82	13	5,920,000	36,250,000	2,870	290 1.023	...	38
Dec	....	..	..	..	..	..	..	..	....	....	.....	.....	108	

PATHOLOGICAL OBSERVATIONS

The kidneys only were obtained after death. They were normal in size, measuring 11.5 × 6 × 4 cm. The capsule was somewhat adherent and when stripped left a finely granular greyish pink surface which was studded with small irregular yellowish points. No hemorrhages were visible. The cut surface showed a cortex of normal width, very opaque and greyish yellow in color. The arteries were not thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically every glomerulus examined in many sections is involved by the inflammatory process. Some are enlarged to twice their normal size, the capillary tuft is infiltrated with leucocytes including polymorphonuclears and the capsular space is filled with a coagulated exudate of fibrin, leucocytes and endothelial cells. In others the same inflammatory lesions are found with accompanying

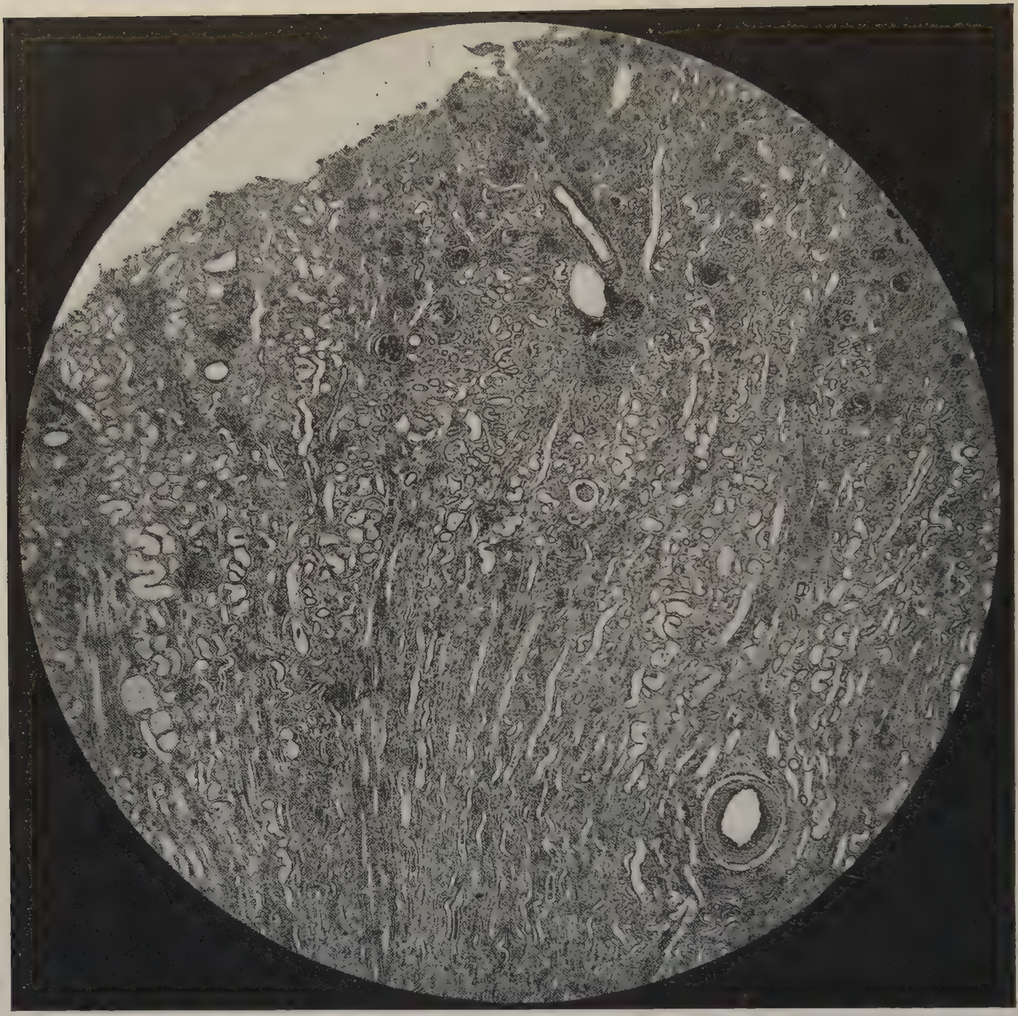

PLATE XV A

The interstitial tissue of the cortex shows a marked irregular proliferation with a resulting collapse and distortion of the tubules. In other regions the latter are dilated. The arteries show a definite thickening of their walls and the irregularity of the surface of the kidney may be recognized.

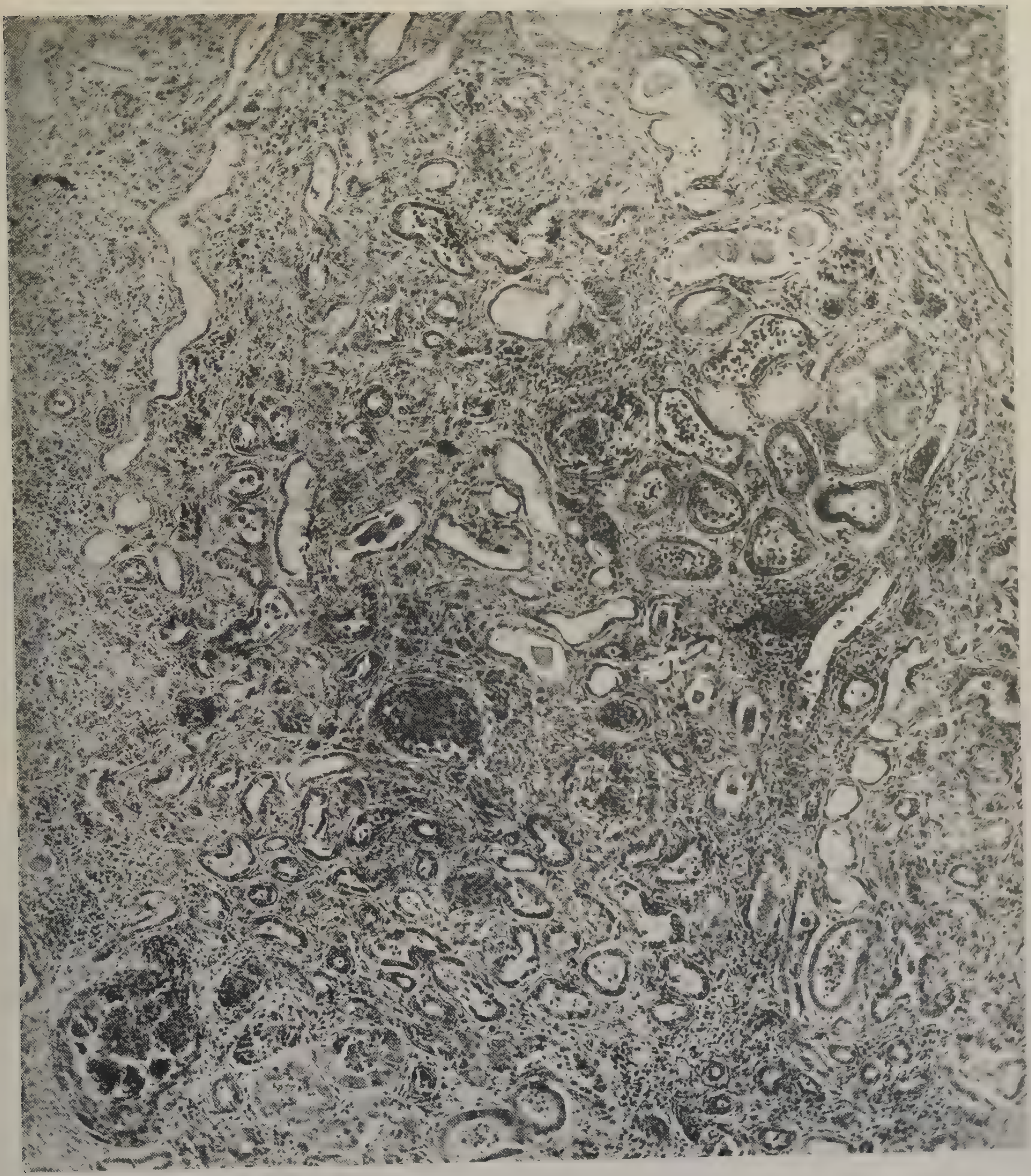

Plate XV b

In the lower left corner is a glomerulus which is almost completely destroyed by the inflammatory process. There is marked leucocytic infiltration not only throughout the interstitial tissue, but the lumens of the tubules as well are filled with polymorphonuclear leucocytes.

organization of the exudate and fibrosis of the tuft. Still others have been transformed into solid masses of collagen in which no capillaries remain.

Tubules. The epithelium of the convoluted tubules and broad ascending limbs of Henle's loops show widespread degenerative lesions. In some the lesions consist of a simple granular degeneration, in others the epithelial cells are generally swollen and filled with large hyaline droplets. In scattered areas the cells are filled with fat droplets of irregular size. There is no frank necrosis of the epithelium in any of the tubules but in many there is considerable desquamation of the lining cells. In such areas there is an irregular regeneration of the epithelium.

In the lumens of the convoluted tubules and occasionally in the limbs of Henle's loop are granular material and leucocytes, many of the latter of the polymorphonuclear type, and more rarely red blood cells may be found. In the straight tubules of the medulla are many casts of all sorts, hyaline, granular and epithelial. An occasional blood cast can be found by careful search.

Interstitial Tissue. Throughout the cortex there is a diffuse and extensive proliferation of the interstitial tissue with an accompanying collapse and atrophy of the tubules. In this tissue there are large areas of heavy leucocytic infiltration, most of the cells being lymphocytes but with a few polymorphonuclear leucocytes.

Arteries. The larger arteries between the cortex and medulla show a moderate fibrous thickening of their intima. The change is not extreme in any of the vessels.

SUMMARY

The kidneys show extensive involvement, the lesions consisting of the early and later stages of an extracapillary glomerulitis, all forms of epithelial degeneration, and the presence of casts of all types. The proliferative changes in the interstitial tissue of the cortex have destroyed a great part of the excretory tissue and profoundly altered the architecture of the kidney.

THE LATENT STAGE

CASE XVI

Patrick F. Aged sixty-six.

Clinical Diagnosis. Hemorrhagic Bright's disease, latent stage.

Duration. Unknown, but probably less than one year.

Etiology. No information.

Course. On October 19, 1921, evidences of the latent stage of a glomerular nephritis were found by examination of the urine. A year before a routine urine examination had failed to disclose any abnormality. During November 1921 the patient died in another hospital.

RELEVANT CLINICAL DETAILS

In May 1921 the patient came to the out-patient department of the hospital because of blurring of vision. Choroiditis with pronounced retinal arteriosclerosis was found. General examination disclosed an aneurysm of the aortic arch and descending aorta, general arteriosclerosis, a blood pressure of 160 systolic and 85 diastolic, and an absence of any indication of cardiac enlargement. The Wassermann reaction was strongly positive. No albumin or casts were reported on routine urine examination.

On October 17, 1921, the patient was admitted to the hospital on account of recurrent hemoptysis. His vision had greatly deteriorated. The Wassermann reaction was still positive in spite of intensive treatment. Routine examination of the urine showed the presence of a little albumin and of some red blood cells. A concentration test on October 19, 1921, gave a volume of 105 c.c. and a specific gravity of 1.019. The rate of protein excretion was 50 mg. per twelve hours. The number of casts was 112,500 per twelve hours. Of these casts 82 per cent were blood casts, 8 per cent were epithelial, 6 per cent granular and 4 per cent hyaline. No cellular counts were made, but there were many red blood cells. The blood urea concentration was 43 mg. per 100 c.c. A determination of the amount of renal tissue showed that 44 per cent of the estimated normal amount of kidney tissue was still functioning. It was concluded that the patient was in the latent stage of a glomerular nephritis. The renal lesion had, however, relatively little clinical importance in comparison with the vascular lesions from which he died soon afterwards in another hospital.

PATHOLOGICAL OBSERVATIONS

Autopsy showed syphilis of the aorta, an aneurysm of its arch and a general arteriosclerosis. There was also present a chronic ulcerative endocarditis with embolic obstruction of arteries to the skin of the hand and of the superior mesenteric artery.

The kidneys were normal in size. Their capsules stripped easily, leaving a smooth surface of greyish pink color. An occasional petechial hemorrhage was present. The cut surface showed indistinct markings. The renal arteries were normal.

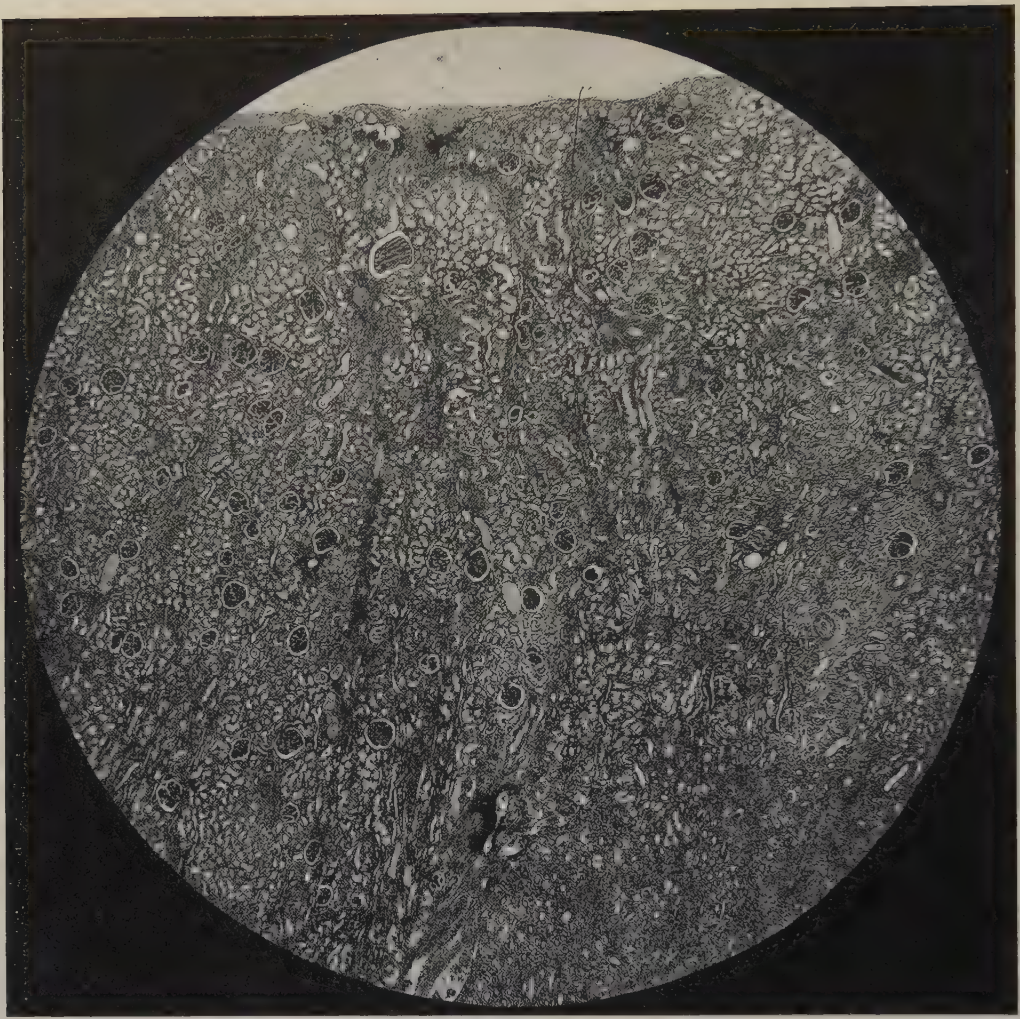

PLATE XVI A

The glomeruli are somewhat prominent as a result of the slight infiltration of their tufts with leucocytes. The interstitial tissue shows a slight proliferation but there is no marked atrophy of the tubules. Some of the arteries are slightly thickened.

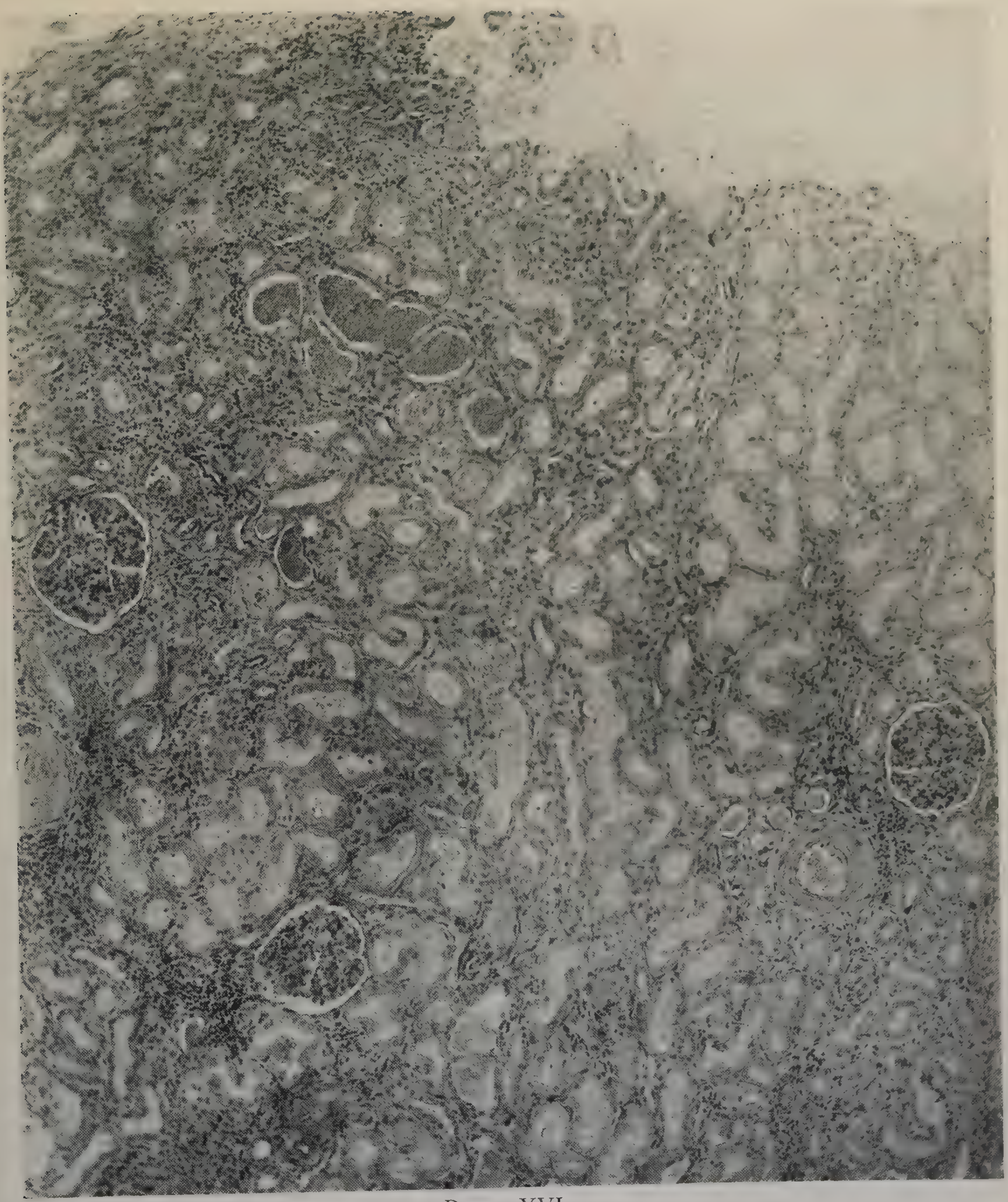

Plate XVI b

A few polymorphs may be seen in the glomerular tufts. The casts seen at the upper middle portion of the figure are blood casts. There are moderate degenerative changes in the tubular epithelium and a diffuse infiltration of the interstitial tissue with leucocytes, among these cells being many polymorphonuclears.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all the glomeruli appear normal to low magnification. There is no definite increase in the nuclei of the tuft, no fibrosis and Bowman's capsule is free of exudate or red blood cells. Careful search with higher magnification, however, shows an infiltration of the tuft with polymorphonuclear leucocytes, these cells being few in number and scattered diffusely through the intracapillary tissue. No focal capillary emboli are present, either recent or old.

Tubules. The epithelium of the convoluted tubules of the cortex shows a mild recent cloudy swelling and their lumens contain granular material. There are also present red blood cells and blood casts. Occasionally a tubule is found which contains polymorphonuclear leucocytes embedded in the granular material which fills its lumen, and a moderate number of hyaline and granular casts are present in the straight tubules of the medulla. In the small cellular scars scattered irregularly throughout the cortex the tubules are irregular in shape and their epithelium is of the atypical regenerated type.

Interstitial Tissue. Throughout the cortex there is a moderate slightly irregular proliferation of the intertubular connective tissue. The new-formed tissue is quite cellular, being made up of fibroblasts with a few collagen fibrils and a diffuse scattering of leucocytes. The majority of these cells are lymphocytes, but polymorphonuclears may also be found in considerable numbers.

Arteries. The larger arteries show a moderate fibrous thickening of their intima. The medium sized interlobular arteries and smaller branches are normal.

SUMMARY

There is a low grade, but still active inflammatory process in the glomeruli and interstitial tissue, as evidenced by the polymorphonuclear infiltration and the escape of red blood vessels from capillaries. The tubular epithelium shows a mild parenchymatous degeneration. The arteries are essentially normal.

CASE XVII

Floyd McC. Aged thirty-two.

Clinical Diagnosis. Hemorrhagic Bright's disease, latent stage.

Etiology. Streptococcus viridans.

Duration. Unknown but probably less than five months.

Course. Died of streptococcal endocarditis after a typical course which extended over a period of five months.

Only one urine examination was made in this case, five days before death. Five months previously he had commenced to suffer from chills and fever, which had continued with only occasional intermissions. The heart was enlarged and a diastolic murmur was heard at the base. The blood pressure was 110 systolic and 70 diastolic. There was no edema. The spleen was slightly enlarged. No evidences of skin emboli were seen. A growth of streptococcus viridans was obtained from one blood culture. The urine had a normal appearance but contained 27,600,000 red blood cells in twelve hours. There were 7,140,000 white blood cells and epithelial cells. The rate of protein excretion was 320 mg. per twelve hours. In the twelve hour period 211,000 casts were eliminated. Of these 5 per cent were blood casts, 10 per cent epithelial, 25 per cent granular, 5 per cent waxy and 55 per cent hyaline.

PATHOLOGICAL OBSERVATIONS

Autopsy showed a chronic endocarditis with a resulting aortic and mitral stenosis in which had occurred a more recent infection with streptococcus hemolyticus so that both the aortic and mitral valves were covered with recent thrombotic vegetations. There was also present a recent fibrinous pericarditis. The heart was about twice the normal size. The spleen measured 17 × 12 × 6 cm. and contained a large septic infarct.

The left kidney measured 15 × 7 × 4 cm., the right 14 × 7 × 4 cm. The capsules of both stripped easily, leaving a smooth surface which was rather congested, mottled with lighter areas and presented a moderate number of petechial hemorrhages. On the cut surface the cortex was opaque and swollen and the pyramids much congested. The arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. In spite of the fact that many of the glomerular tufts contain large emboli of bacteria, there is very little reaction on the part of their tissues. In some of Bowman's spaces there is a granular exudate and occasionally leucocytic infiltration of the glomerular tuft is seen, but the majority are essentially normal.

Tubules. The epithelium of the convoluted tubules and of the broad ascending limbs of Henle's loops shows a marked cloudy swelling, with in places definite necrosis and desquamation. In the area of the infarct this necrosis is quite extensive and at its edges regeneration is seen. Occasionally a group of tubules is found

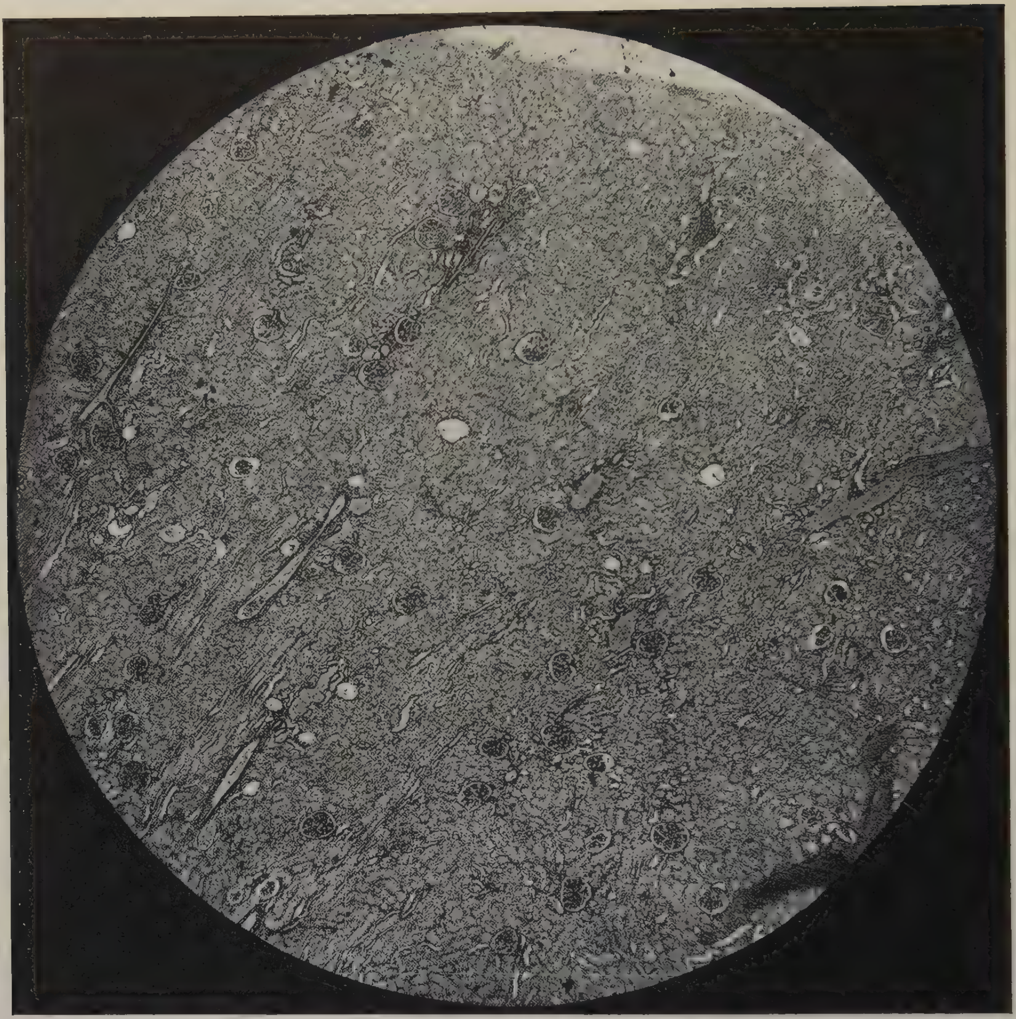

Plate XVII a

Except for a diffuse infiltration of the interstitial tissue with polymorphonuclear leucocytes, the details of which cannot be seen at this low magnification, the general appearance of the section is essentially normal. Some of the large vessels are dilated.

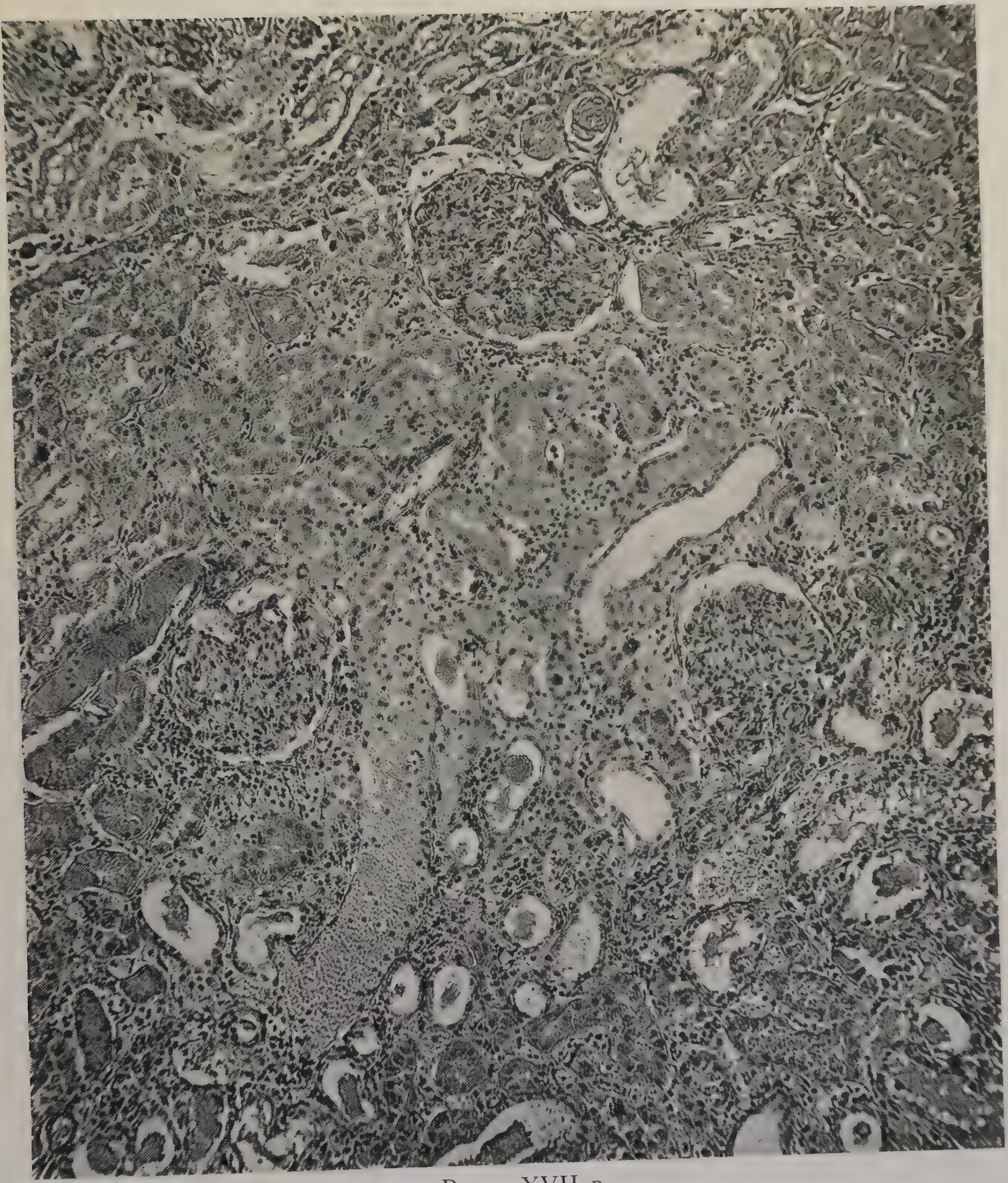

Plate XVII b

Throughout the interstitial tissue as well as in the glomerular tufts may be seen the leucocytic infiltration. Most of the cells are of the polymorphonuclear type. There is a marked cloudy swelling of the epithelial cells.

containing red blood cells and the lumen of others is filled with hyaline and granular casts.

Interstitial Tissue. There is a moderate but definite edema of the interstitial tissue and a diffuse infiltration, particularly in the cortex, with leucocytes. The majority of these cells are polymorphonuclears and in localized areas necrosis of the tissue is seen with definite abscess formation. There are a few scattered areas of hemorrhage throughout the interstitial tissue. No productive inflammatory changes are present.

Arteries. The arteries except for a slight fibrous thickening are normal.

SUMMARY

The kidneys show a diffuse acute suppurative inflammatory process and abscess formation most pronounced in the interstitial tissue and accompanied by severe epithelial degeneration. The condition can perhaps be best summarized as an "acute septic nephritis."

CASE XVIII

John M. Aged fifty.

Clinical Diagnosis. Hemorrhagic Bright's disease, latent stage.

Etiology. Secondary infection in a tuberculous sinus.

Duration. Eleven months.

Course. Initial stage was typical with bloody urine, edema and hypertension, and was followed by an active stage which slowly decreased to latency. A recurrence of infection was associated with some increase in activity. The patient died of sepsis before any indications of the terminal stage had appeared.

RELEVANT CLINICAL DETAILS

There is no doubt that the renal lesion was observed from the very commencement of the initial stage because the patient had already been under close observation and numerous routine urine examinations had failed to disclose any abnormality. In 1907 he had first suffered from stiffness and pain in his right knee. In 1918 a cold abscess had formed and had been opened. Four months later he entered the hospital and his knee joint was resected. However a sinus formed and he was under treatment by vaccines when on April 12, 1920, he noticed slight breathlessness on exertion. On examination he was found to have a slight edema of of the face and pitting edema in the legs. The blood pressure was 162 systolic and 104 diastolic. The blood urea concentration was 163 mg. per 100 c.c. The urine was grossly bloody. No counts were made but it was noted that there was a large amount of sediment consisting mainly of partially lyzed red blood cells and of white blood cells and epithelial cells but also with a considerable number of casts. During the first few days no blood casts were found, but thereafter they were constantly present. Table xxv shows the rate of decrease in blood urea concentration which followed.

Only qualitative observations were made on the sediment in the spring of 1920 but the notes show that considerable numbers of fatty casts were present after the initial stage had passed so it seems likely that an active stage had supervened, although there was no edema. But after four months the casts were not so numerous and the lesion had obviously become latent.

On September 26 the temperature suddenly rose and he complained of pain in his leg. There was redness and swelling in the region of the resection wound. The urine which previously had been clear again became red with blood and contained a large number of casts. The blood pressure however remained normal and there was no reappearance of edema. The sinus was opened up, a metal spike was removed from the bone, and the wound was drained. But infection nevertheless continued and there was almost constant fever. There was no indication, however, of any rapid destruction of the kidney, for the amount of functioning renal tissue as measured by successive ratio tests remained fairly constant, and the blood urea concentra-

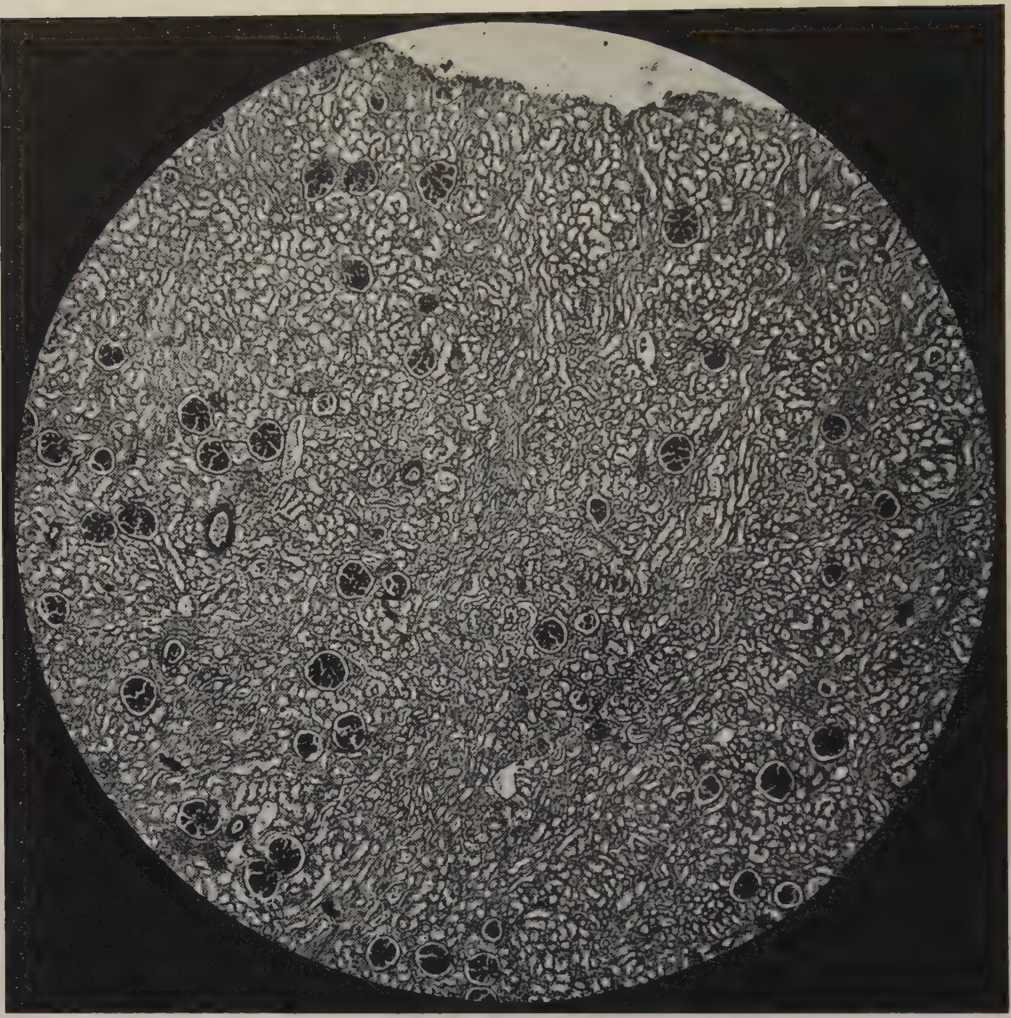

Plate XVIII a

The glomeruli are prominent as a result of fibrosis in them. There is a slight evenly distributed proliferation of the connective tissue of the framework of the kidney but no marked alteration of its architecture.

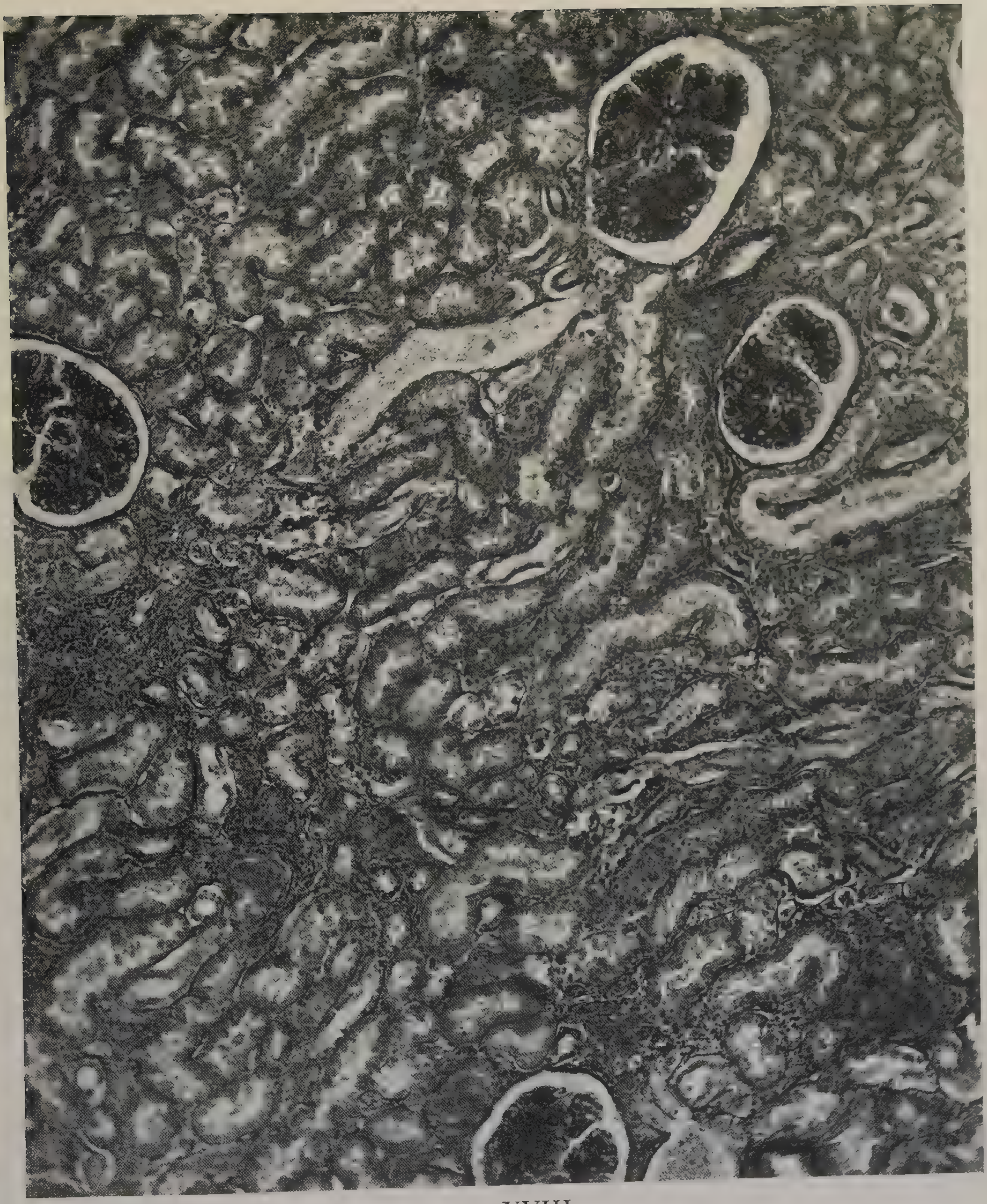

Plate XVIII b

In the glomeruli there is a marked proliferation of connective tissue which obliterates the capillary bed. Throughout the interstitial tissue are seen areas of leucocytic infiltration. Except for cloudy swelling the tubular epithelium is well preserved.

TABLE XXV

Day from Commencement of Lesion	*Blood Urea mg. per 100 c.c.*
7	163
10	142
13	128
14	114
16	92
20	58
28	43
42	36
47	32
51	25
63	30
75	27
91	35
109	41
169	30
201	32
251	36
282	27

tion remained within the upper limits of normality. The ratio results are shown in Table XXVI:

TABLE XXVI

Date	*Amount of Functioning Tissue. Per Cent of Normal*
Aug. 6, 1920	40
Aug. 10, 1920	48
Aug. 19, 1920	43
Sept. 8, 1920	43
Nov. 10, 1920	40
Dec. 10, 1920	37

On December 23 the leg was amputated through the middle of the thigh. After the operation the urine contained large amounts of pus. On January 18, 1921, the infected stump was removed at the hip, but the patient died of sepsis on February 6, 1921.

PATHOLOGICAL OBSERVATIONS

Healed tuberculosis lesions were found at autopsy at the apices of both lungs and in the peribronchial lymph glands. Except in the kidneys no other significant lesions were present. A healed tuberculosis was found in the right kidney which had been practically completely destroyed. It was reduced to a thin shell of fibrous partly calcified connective tissue about 0.5 cm. thick which enclosed a mass of yellowish pasty detritus. The irregular cavity thus enclosed connected with the pelvis of the kidney which was filled with similar material. The ureter was thickened and fibrous and completely obliterated throughout its entire length.

The right kidney was large, measuring 16 × 7 × 4 cm. Its capsule stripped easily, leaving a smooth greyish pink surface. The cut surface presented a wide and rather opaque surface but was otherwise normal. The renal arteries were slightly thickened.

MICROSCOPICAL EXAMINATION

Left Kidney. The left kidney consists of dense fibrous connective tissue which is hyaline in places and densely infiltrated with round cells. In this fibrous tissue are dilated cystic tubules lined by an atrophied epithelium and filled with hyaline material. There are also the scattered remains of glomeruli, either dilated or collapsed and fibrous. No tubercles or caseous areas are present. The section of the ureter shows the same chronic inflammation of its wall. The mucosa is destroyed and the lumen is completely filled with detritus in which are cholesterin crystal spaces.

Right Kidney. *Glomeruli.* No recent inflammatory lesions are present in the glomeruli, but all show the late effects of an earlier inflammatory process. There is a very considerable development of fibrous connective tissue between the capillaries so that the tuft is considerably thickened and the capillaries are in part obliterated. The lesion is limited to the tuft, however, as Bowman's space is empty and there are no capsular adhesions.

Epithelium. There is a very definite cloudy swelling of the epithelium of the convoluted tubules, but little evidence of frank necrosis. The tubules throughout the entire kidney are well preserved as to shape and size. An occasional hyaline cast is seen in the straight tubules.

Interstitial Tissue. Except for an occasional small scar in the cortex the interstitial tissue is normal and shows no increase in its fibrous tissue nor round cell infiltration.

Arteries. There is a considerable fibrous thickening of the intima of the larger arteries that lie between the cortex and medulla.

SUMMARY

Since the left kidney was completely destroyed and shut off from the urinary tract by the obliteration of the lumen of the ureter it played no part in the urinary findings. The right kidney shows the results of a latent or perhaps completely healed intracapillary glomerulitis associated with mild but active degenerative changes in the epithelium. There is also a moderate renal arteriosclerosis which has not, however, produced much change in the kidney parenchyma.

CASE XIX

Mark T. Aged forty-five.

Clinical Diagnosis. Hemorrhagic Bright's disease, latent stage.

Etiology. Streptococcus viridans (ulcerative endocarditis).

Duration. Unknown but probably less than fourteen months.

Course. Symptoms of cardiac disease for fourteen months. Died soon after admission to the hospital.

RELEVANT CLINICAL DETAILS

The patient came to the hospital in an ambulance because he was unable to walk on account of dyspnea. Fourteen months before he had first noticed palpitations and a few months later he had suffered from dyspnea on exertion and swelling of his ankles. During the last five months he had been too ill to work. Examination showed an enlarged heart with signs of pericarditis. The blood pressure was 112 systolic and 55 diastolic. He died soon after admission.

The urine contained a sufficient number of red blood cells to give it a distinctly smoky appearance, but there was no marked increase in white blood cells or epithelial cells. The number of casts was not large. There were 6 per cent blood casts, 2 per cent waxy casts and 92 per cent hyaline casts.

PATHOLOGICAL OBSERVATIONS

Autopsy showed a moderate edema of the hands and ankles and small collections of clear fluid in the serous cavities. The heart was twice the normal size and at the aortic orifice the valves were ulcerated and covered with recent thrombotic masses in which were gram-positive diplococci.

The kidneys measures 12 × 6 × 4 cm. The capsule stripped easily, leaving a smooth surface in which were a great number of petechial hemorrhages. The cortex on the cut surfaces was opaque. The medulla and pelvis were normal. The renal arteries as well as the arteries in general showed no significant lesions.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are swollen with in most cases an almost complete obliteration of Bowman's space. The space of those in which it still persists is filled with granular material as no capsular proliferation or inflammatory exudate is present. In the swollen tufts one finds occasionally hyaline thrombi in the capillaries, as well as more frequent collections of polymorphonuclear leucocytes and edema between the capillaries. No productive inflammatory lesions are present.

Tubules. The epithelium of the convoluted tubules of the cortex and the broad ascending limbs of Henle's loops show a very marked cloudy swelling. Only occasionally is the lesion more severe, though there is some fatty degeneration and desquamation in places. The lumens contain granular material and in isolated spots many recently shed blood cells are found. As a rule this material is not organized into definite casts, though a few granular, hyaline and blood casts can be found in the straight tubules of the medulla.

Interstitial Tissue. Scattered through the cortex are small foci of round cell infiltration situated as a rule in the proximity of a glomerulus. There is no significant proliferation of the fibrous tissue of the framework of the kidney however.

Arteries. There is a moderate fibrous thickening of the intima of the larger arteries.

SUMMARY

The kidneys show an early and active glomerulitis of the intracapillary type and marked epithelial degenerative lesions.

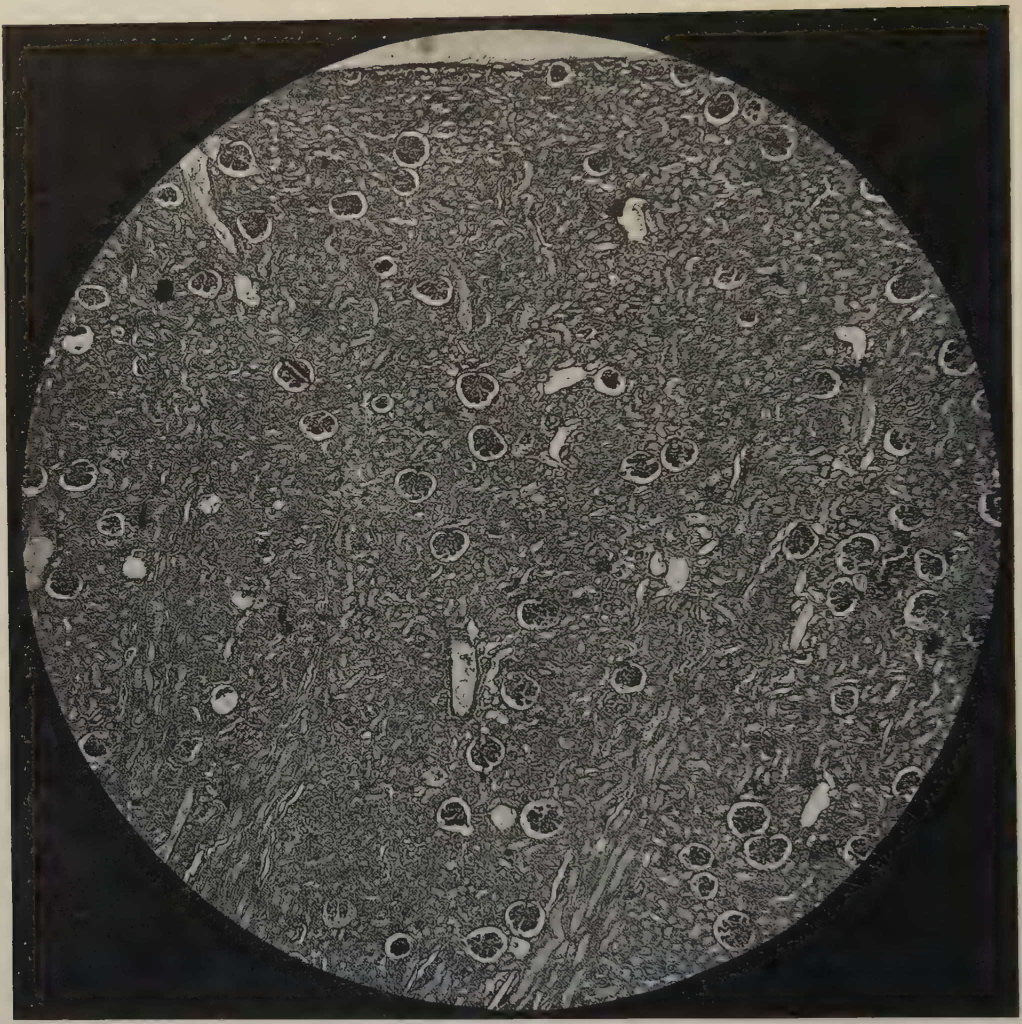

Plate XIX a

The glomeruli are swollen. The interstitial tissue shows only slight proliferative changes and the tubules are therefore normally arranged.

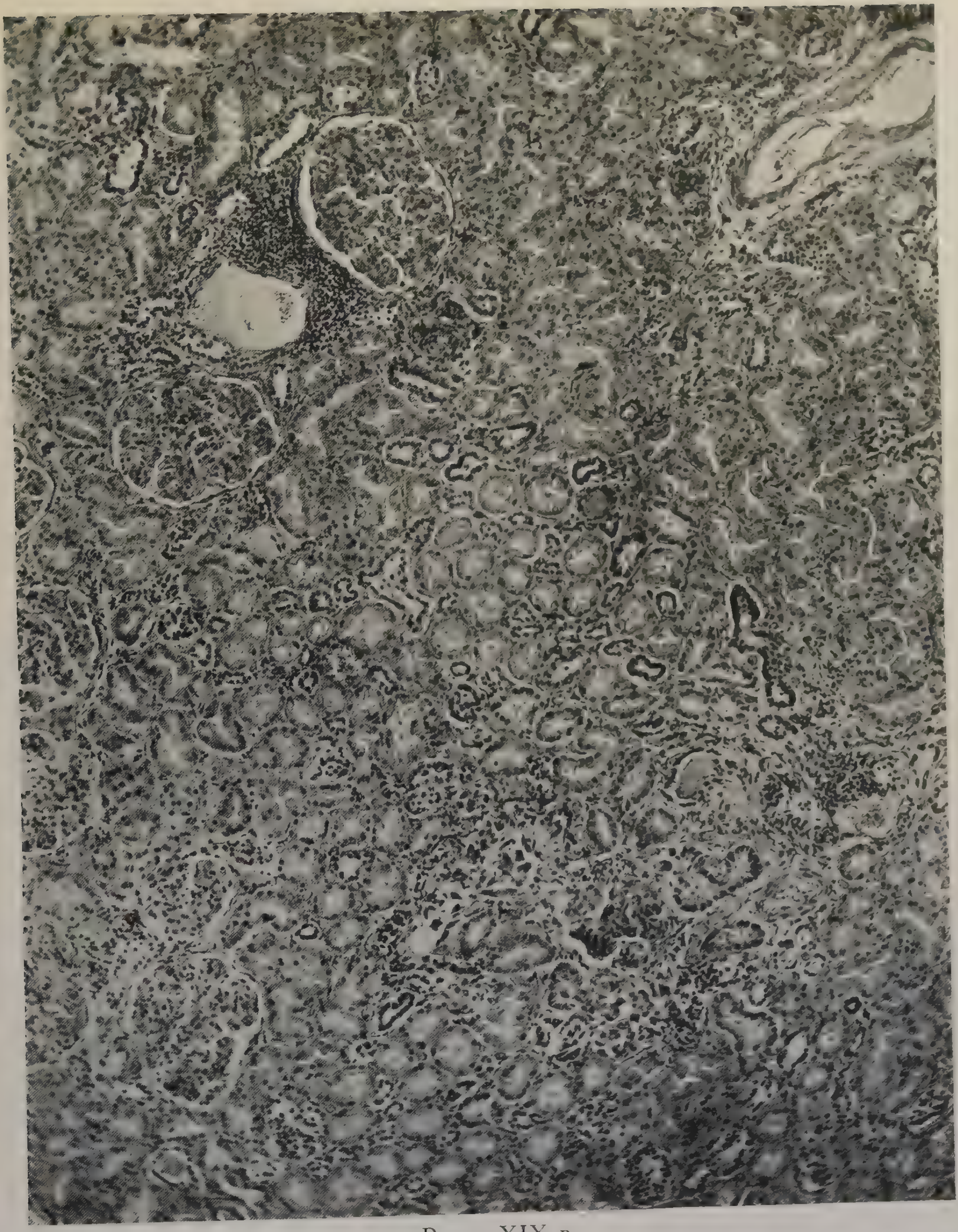

PLATE XIX B

There is an increase in nuclei in the glomerular tuft. Scattered areas of leucocytic infiltration are seen throughout the interstitial tissue. Degeneration of the epithelial cells is also plainly seen.

CASE XX

Thomas Z. Aged forty-five.

Clinical Diagnosis. Hemorrhagic Bright's disease, latent stage.

Etiology. Finger infection.

Duration. Five months. Observed throughout the whole course.

Course. Typical initial stage merging into a latent stage which was terminated by sudden death from coronary artery thrombosis.

RELEVANT CLINICAL DETAILS

The patient was first seen in consultation. He stated that on April 6, while engaged in his work of curing beef, he had pierced his left finger with a hollow needle through which a 40 per cent solution of potassium nitrate was being pumped. Very soon afterwards his finger became very much swollen and was so painful that all that night he could not sleep. Next morning the finger "burst" and clear fluid ran out. The pain though lessened still persisted and five days later was again severe when the finger and the palm of his hand became red and swollen. Next day he noticed that red lines had appeared on his forearm. This inflammation gradually subsided but on April 29 he suffered from some shortness of breath on exertion and when he woke next morning he found that his face was swollen. Next day, when first seen, there was very evident edema of the face and a moderate degree of edema of the legs. The blood pressure was 185 systolic and 115 diastolic. The blood urea concentration was 98 mg. per 100 c.c. On the following morning a twelve hour collection of night urine was obtained. The volume was 238 c.c. and the specific gravity 1.020. The amount of protein was 2400 mg. The number of casts in the twelve hours' urine was 1,190,000, and there were 625,000,000 red blood cells and 57,000,000 white blood and epithelial cells.

The following was the differential cast count:

Casts	*Per Cent*
Blood	25
Epithelial	11
Granular	17
Fatty	6
Waxy	4
Hyaline	37
Renal failure	0

On the basis of these observations it was concluded that he was in the initial stage of hemorrhagic Bright's disease.

He was not seen again until twenty-seven days later when he was referred for treatment. He said that the edema had disappeared after three days in bed, and that he had felt quite well except that on two different occasions he had experienced an acute pain in his chest and had become unconscious. In one of these attacks he was seen by his doctor who found him in a stuporous condition and cyanosed. The blood pressure was 190 systolic and 110 diastolic. Some râles were heard at both bases, but no abnormality was detected when his heart was examined. On this occasion 300 c.c. of blood were removed and he quickly became conscious. From the second attack, which occurred two days later, he recovered without treatment. When examined on his second visit there was no trace of edema. The blood pressure was 130 systolic and 70 diastolic. Physical examination failed to show any abnormality beyond some thickening and tortuosity of the brachial arteries. After abstention from fluid during the day the twelve hours' night urine had a volume of 459 c.c. with a specific gravity of 1.018. It was obvious that the urine still contained blood and 675,000,000 red blood cells and 59,000,000 white blood cells and epithelial cells were counted. The amount of protein had decreased to 610 mg. in twelve hours. There was 333,000 casts with the following distribution:

Casts	*Per Cent*
Blood	33
Epithelial	12
Granular	4
Hyaline	51

Two days later, thirty-four days from the time he first noticed the swelling of his face, generally similar results were obtained but the rate of protein excretion had fallen to 511 mg. per twelve hours, and the number of red cells was 225,000,000 with 13,000,000 white blood and epithelial cells.

On that day the ratio between the rate of urea excretion and the blood urea concentration was determined over three hourly periods after the administration of urea and of large amounts of water. The result showed that 68.4 per cent of the amount of renal tissue to be expected from his calculated body surface was still functioning.

The diminution in the amount of blood and the disappearance of fatty casts and of fatty epithelial cells suggested that the activity of the initial stage and the degenerative element in the renal lesion were subsiding.

On the forty-sixth day and fifty-fifth day after the oset the counts shown in Table XXVII were made.

In the meantime the patient had been taught how to calculate food values and was cooking for himself and taking a diet which contained approximately 50 gm. of protein, 2500 calories and a minimal amount of salt. Twenty-four-hour analyses of the urine showed that he was succeeding fairly well as regards salt exclusion and was getting a sufficient amount of food, for his weight increased by 14 lbs. over a period of one hundred two days without any reappearance of edema. His blood pressure was at times as low as 120 systolic and 75 diastolic but on one day was as high as 153 systolic and 107 diastolic. He had no recurrence of pain in his

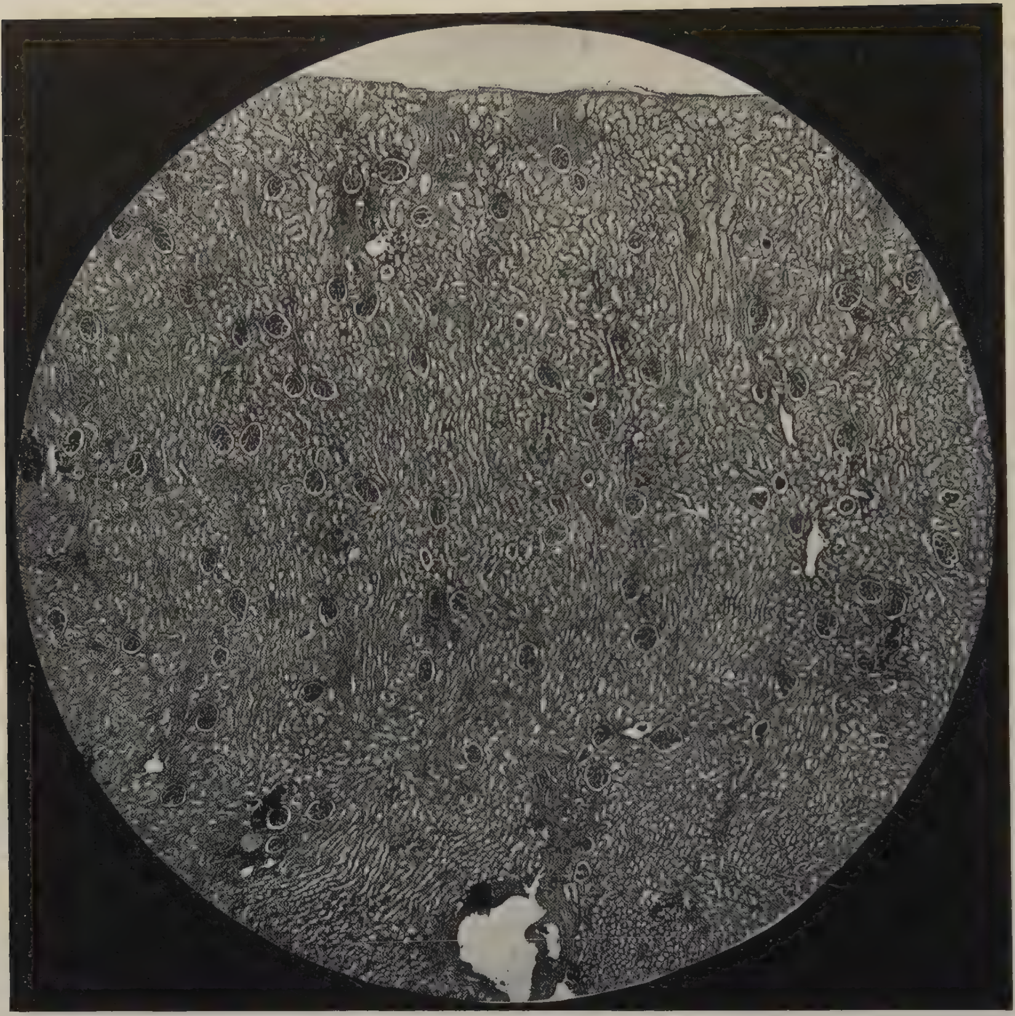

Plate XX a

The glomeruli appear essentially normal and the interstitial tissue, except for an arteriosclerotic scar at the surface of the organ, is not markedly altered. As a result this low power photograph does not show any very significant lesions.

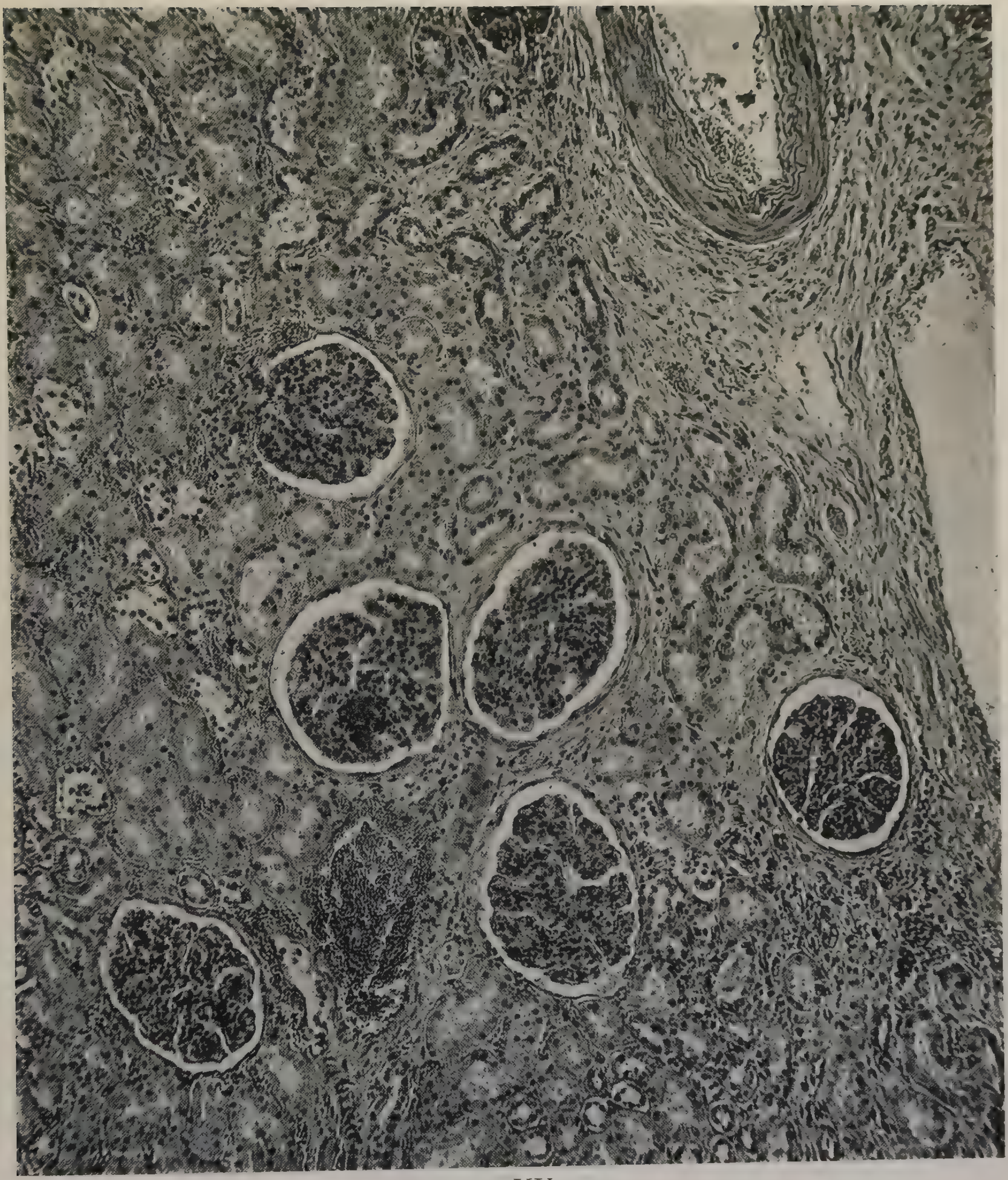

Plate XX b

There is a definite increase in the cellular elements of the tufts. At the upper right hand portion of the figure in the neighborhood of an artery there is an area of connective tissue proliferation and round cell infiltration. The epithelium of the tubules shows only slight degenerative changes. (Cf. Plate xciii.)

chest and said that he felt perfectly well. He was now obliged to return to work but was given an easy job.

TABLE XXVII

	46th day	55th day
Volume per 12 hours	477	600
Specific gravity	1.014	1.016
Casts per 12 hrs	252,000	208,000
R.B.C. per 12 hrs	195,000,000	176,000,000
W. and Ep.C. per 12 hrs	13,000,000	5,400,000
Protein, mg. per 12 hrs	695	324
Blood casts, per cent	24	20
Epithelial casts, per cent	4	10
Granular casts, per cent	4	0
Hyaline casts, per cent	68	70

On the ninety-sixth day after the onset the rate of protein excretion had fallen to 65 mg. per twelve hours and the number of casts to 33,000. There were now only 85,000,000 red cells, and 4,700,000 white and epithelial cells. It was clear that he was now definitely in the latent stage of the disease.

On the one hundred seventeenth day after the onset the protein excretion was 29 mg. per twelve hours. Only 19,100 casts were counted of which 15 per cent were blood casts. The number of red cells in twelve hours was 68,000,000 and there were 1,200,000 white blood and epithelial cells.

On the day before he died, the one hundred sixty-fifth day after the onset, the volume of urine for twelve hours was 329 c.c. with a specific gravity of 1.030. Only 12 mg. of protein were present in the twelve hours' urine. The number of casts was 27,200 and there were 40,100,000 red blood cells and 1,400,000 white and epithelial cells.

Next day he came home at night and said that he had been well but now had some abdominal discomfort. He went to bed and while sitting up suddenly fell backward dead.

PATHOLOGICAL OBSERVATIONS

At autopsy a general arteriosclerosis of moderate degree was found with a pronounced involvement of the coronary arteries. A recent thrombus was present in the left coronary artery. The cardiac muscle showed a diffuse scarring with connective tissue but no recent necrosis. The valves were normal. The remaining organs showed nothing significant.

The kidneys were of normal size, measuring 12 × 6 × 4 cm. The capsule stripped easily leaving a surface which presented a few small scattered scars. The cut surface showed nothing abnormal and the renal arteries were slightly thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. The gomeruli show few signs of an active process. There is, however, a very definite cellular increase within the capillary tuft, as is evidenced by the increase in nuclei of fibroblasts and round cells, but there is no increase in fibrous tissue in them. The capsular space is empty and there are no collections of exudate or blood or endothelial proliferation.

Tubules. The epithelial cells of the convoluted tubules and broad ascending limbs of Henle's loop are normal. In the collecting tubules an occasional hyaline cast is found and by careful search through many sections a few blood casts may be discovered.

Interstitial Tissue. Throughout the cortex there are scattered a few small fibrous scars in which is some round cell infiltration. The tubules in these regions are somewhat atrophied. The amount of cortical tissue destroyed by the scars is however very small.

Arteries. There is a moderate fibrous thickening of the intima of the arteries.

SUMMARY

The kidney shows only slight lesions which consist of traces of a former glomerulitis of the intracapillary type, and a moderate arteriosclerosis of the renal arteries with slight scarring of the cortex. Active processes are evidenced by the moderate number of casts, including an occasional blood cast.

THE TERMINAL STAGE

CASE XXI

Percy B. Aged thirteen.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Etiology. Unknown.

Duration. Unknown. Observed during the last two months.

Course. In April 1926 he began to complain of headache which became gradually more frequent and severe, but it was not until a year later that a doctor was consulted who found that the urine contained protein and that the systolic pressure was 210. He was seen in June 1927 just after his eyesight, which had been blurred for some months, was entirely lost. The urine contained about 5,000,000 red blood cells per twelve hours and renal failure casts were present. The blood urea concentration rose steadily and he died in uremia on August 30, 1927.

RELEVANT CLINICAL DETAILS

The boy had lived all his life alone with his father in a remote part of the country. He was an active nervous child but healthy. The only serious illness occurred in 1919 when he was four years old but its nature is uncertain. For a week he had a high fever and was quite weak for a month or so afterwards. From that time until the commencement of his symptoms he had seemed to his father to be entirely well and happy.

But in April 1926, when he was twelve years old, he woke one morning complaining that he had a pain over his forehead. Although this soon passed off it recurred after a few weeks and thereafter these headaches came more and more frequently and with greater severity. A year later he told his father that he sometimes saw things double, and he was then taken to a doctor in the nearest town. He was found to have protein in his urine and a systolic pressure of 210. He was kept in a hospital for three weeks but at the end of that time he complained that his vision was blurred. The headaches became extremely severe and were now accompanied by vomiting. On the way down in the train to San Francisco he had a particularly bad headache and lapsed into a semicomatose state. When he had partially recovered he was completely blind.

He was seen first on June 24, 1927. He was only semiconscious, pale and undernourished. There was definite evidence of cardiac enlargement. The blood pressure was 205 systolic and 135 diastolic. The eye-grounds showed a neuroretinitis with extensive exudate and hemorrhages which was followed in a few days by a widespread bilateral retinal detachment.

The patient never regained full consciousness but seemed to be free from pain. The blood pressure slowly rose to 240 systolic and 167 diastolic but then fell until shortly before death it was 155 systolic and 140 diastolic. On August 19 a left otitis media drained spontaneously. On August 24 he was deeply comatose and the skin was covered with petechial hemorrhages. On August 29 there were tonic muscular contractions. He died on August 30, 1927.

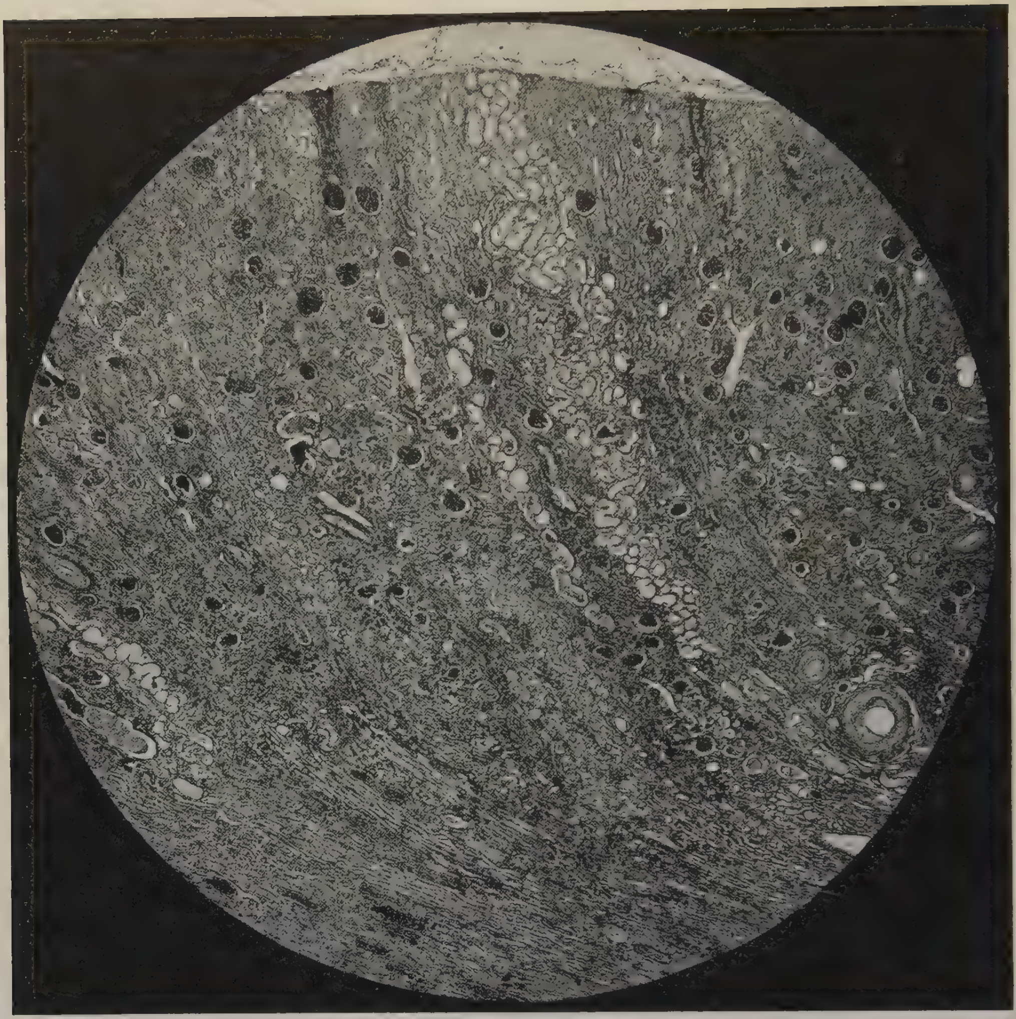

PLATE XXI A

There is a marked proliferation of the connective tissue of the cortex with widespread destruction and atrophy of the tubules. Clusters of them, however, remain either hypertrophied, as seen near the surface of the organ, or dilated and filled with casts. The glomeruli appear as dark spots in various stages of inflammatory destruction. The arteries are markedly sclerotic.

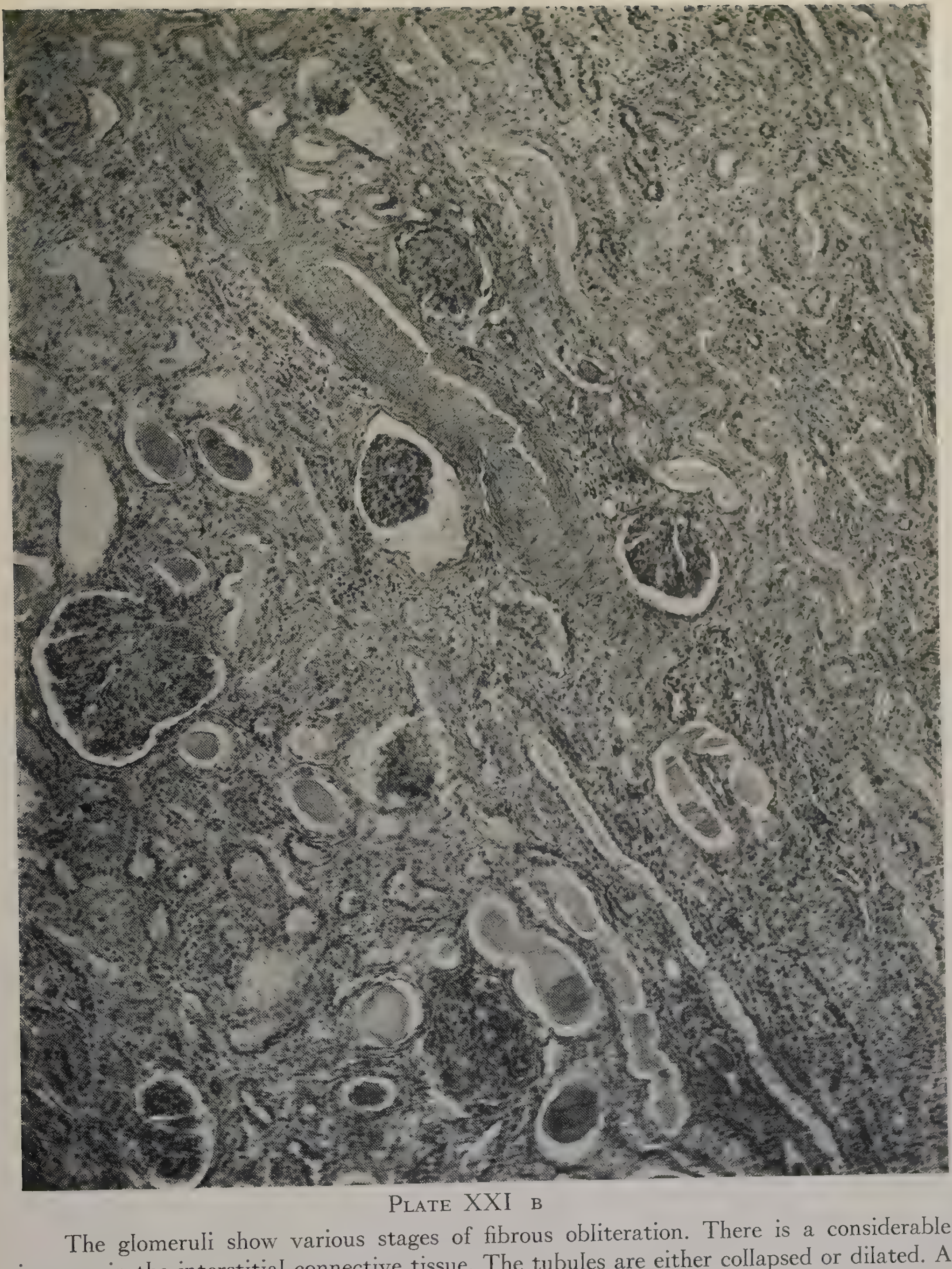

PLATE XXI B

The glomeruli show various stages of fibrous obliteration. There is a considerable increase in the interstitial connective tissue. The tubules are either collapsed or dilated. A small artery which is considerably thickened is also seen. (Cf. Plate XCVIII.)

A timed collection of urine was obtained on June 24. The twelve hours' volume was 495 c.c. with a specific gravity of 1.011. There were 2605 mg. of protein per twelve hours. The number of casts was 111,000 and 14 per cent of these were renal failure casts. The blood urea concentration on that day was 74 mg. per 100 c.c. The number of red blood cells per twelve hours was 5,000,000 and there were 2,500,000 white blood cells and epithelial cells. It seemed likely therefore that we were dealing with the terminal stages of a hemorrhagic nephritis with unusually severe extrarenal vascular lesions. Only one other timed collection of urine was obtained. This contained only 575,000 red blood cells per twelve hours. The blood urea concentration rose steadily and incontinence of urine prevented any further studies.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a chronic suppurative tonsillitis and an acute otitis media. The kidneys were normal in size. Their capsules stripped easily, leaving a fairly smooth greyish pink surface. No definite petechiae could be seen. The cut surface showed indistinct markings. The renal arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli show a definite increase in nuclei and among these cells may be found an occasional polymorphonuclear leucocyte. In some, about one-third the total number, there is a definite increase in the connective tissue of the tuft, varying from a few strands of collagen to complete hyalinization of its structure. Fibrous adhesions are present between the tuft and the wall of Bowman's space, but the latter is free of blood or exudate and no crescents can be found.

Tubules. There is a marked deformity of most of the convoluted tubules of the cortex. They are compressed by the developing interstitial tissue and are lined, or in some cases filled, with atrophied epithelial cells. In other regions they are greatly dilated, forming groups of cyst-like spaces which contain colloid and are lined with a flattened epithelium. In other areas, those comparatively free of fibrosis, the tubules are one and one-half times their normal diameter and are lined with greatly hypertrophied cells. The epithelial cells of the convoluted tubules and the broad ascending limbs of Henle's loop show varying degrees of cloudy swelling. In the majority of instances this is of the finely granular type, but in scattered areas the cells are filled with larger colloid droplets of the "chronic" type of degeneration. The lumens of all are filled with granular material, hyaline or granular casts, masses of polymorphonuclear leucocytes and in the collecting tubules are many large renal failure casts. No red blood cells are found, but the epithelial cells of many of the convoluted tubules and the broad ascending limbs of Henle's loop are filled with golden brown blood pigment.

Interstitial Tissue. Throughout the greater part of the cortex there is a cellular proliferation of the intertubular connective tissue. There is a diffuse infiltration with round cells, and among these may be found polymorphonuclear leucocytes.

Arteries. There is a moderate but definite fibrous thickening of the intima of the arcuate arteries, and the walls of the interlobular arteries are also somewhat thickened.

SUMMARY

There is an old inflammatory glomerulitis of the intracapillary type which is still active but of only moderate intensity. The marked interstitial proliferation has destroyed the architecture of the cortex. The tubules are collapsed or dilated, and show marked parenchymatous degeneration. The arteries show a moderate sclerosis.

CASE XXII

Frederick B. Aged forty-two.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Twenty years or more. Observed during the last thirteen days.

Etiology. No information.

Course. In 1905 insurance was refused because albumin was found in the urine. Many examinations of the urine were made during the next twenty years and albumin was always found. In 1920 he began to be easily tired by physical exertion but continued his clerical work without interruption until October 16, 1925 when he complained of intermittent abdominal pains and general weakness. These were the first indications of a uremia from which he died nineteen days later.

RELEVANT CLINICAL DETAILS

This patient had worked as a clerk in an insurance office for twenty years. When he was first employed he was asked to take life insurance, but on examination he was told that he need not take a policy because his urine contained albumin. So far as he remembered there had been no preceding illness or infection and as no other abnormality was detected he was continued in the employment of the company. He was constantly meeting doctors in the office and he stated that he was in the habit of asking any new doctor to examine his urine and take his blood pressure. They all found albuminuria but none of them said that his blood pressure was too high. Apparently no very thorough examination was ever made and in particular he could not recall that he was ever told anything about casts or red blood cells in the urine.

From 1905 to 1920 his health was good though for some reason he believed that he was not very robust. In 1920 he suffered from headache in the morning. At that time he had a cough with some expectoration when he woke in the morning. He was told that he had a sinus infection. In a few weeks these symptoms had disappeared.

From 1920 until twenty days before his death in 1925 there were no infections or illnesses of any sort. He was proud of the fact that he had never missed a day from work during his twenty years' employment. Yet from the time of the sinus infection he was conscious that he was no longer able to enjoy the amount of physical exercise to which he had previously been accustomed. He gave up playing golf because it made him too tired. However, he did not observe any shortness of breath on exertion and the casual examinations of his urine and blood pressure which were made from time to time apparently showed no appreciable change.

On October 16, 1925 he experienced abdominal pains of a colicky nature and a sense of general weakness. There was no diarrhea or vomiting but he felt a disinclination for food. During the next three days he felt weak enough to stay in bed but had no special symptoms except for occasional intermittent abdominal pain. He ate very little. On October 19 he was startled by a sudden inexplicable attack of breathlessness which lasted however for only a few minutes. Next day there were several such attacks and on October 21 and 22 he had from ten to twenty. There was no regularity about the time at which they appeared. They would, for instance, sometimes come at night when he was asleep. He had to sit up to get his breath but they only lasted for a few minutes.

He was first seen on October 23. Although he himself had not noticed it there was then a slight edema of the legs. The heart was enlarged to the left. The pulse was very variable in rate but regular in amplitude. The blood pressure was 250 systolic and 150 diastolic. The large arteries were thickened and tortuous. There was no evidence of pulmonary edema but the signs suggested that there might be a small collection of fluid in both pleural cavities. No abnormality was detected on abdominal examination. Shortly after admission he was seen in an attack of paroxysmal dyspnea which came suddenly and as suddenly disappeared. The respiration was polypneic rather than dyspneic. There was no cyanosis. There was no recurrence after the administration of morphine.

On October 24 the blood urea concentration was 126 mg. per 100 c.c. A twelve hours' night urine obtained without water restriction had a volume of 425 c.c. and a specific gravity of 1.014. The rate of protein excretion was 3213 mg. per twelve hours. The number of casts in 12 hours' urine was 170,000. All the casts were of the renal failure type and the great majority were broad. The number of red blood cells in twelve hours was 10,600,000 and there were 1,900,000 white blood cells and epithelial cells.

The uremia progressed rapidly. On October 26 the blood urea had risen to 222 mg. per 100 c.c. On October 31 it was 308 mg. per 100 c.c. On that day he became irrational but for the most part was quiet and drowsy. Bruises appeared on very slight trauma. The reflexes were hyperactive. On November 3 complete anuria set in. There were two generalized convulsions lasting for only a few minutes, but there was constant twitching of various muscle groups. He was now deeply comatose and died early next day.

PATHOLOGICAL OBSERVATIONS

The kidneys only could be examined after death. They were somewhat smaller than normal, averaging 10 × 5 × 3 cm. in size. The capsule stripped with some difficulty, leaving a granular mottled greyish red surface. The cut surface showed indistinct markings and the renal arteries were distinctly thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. None of the glomeruli is normal. About one-half their number are of normal size, but their tufts are obliterated by cellular fibrous connective tissue and infiltration with mononuclear and a few polymorphonuclear leucocytes. Bowman's space is also completely obliterated by fibrous adhesions. The remaining glomeruli are completely fibrous and exist only as small clumps of hyaline collagen in which a few atrophied fibroblasts and leucocytes remain.

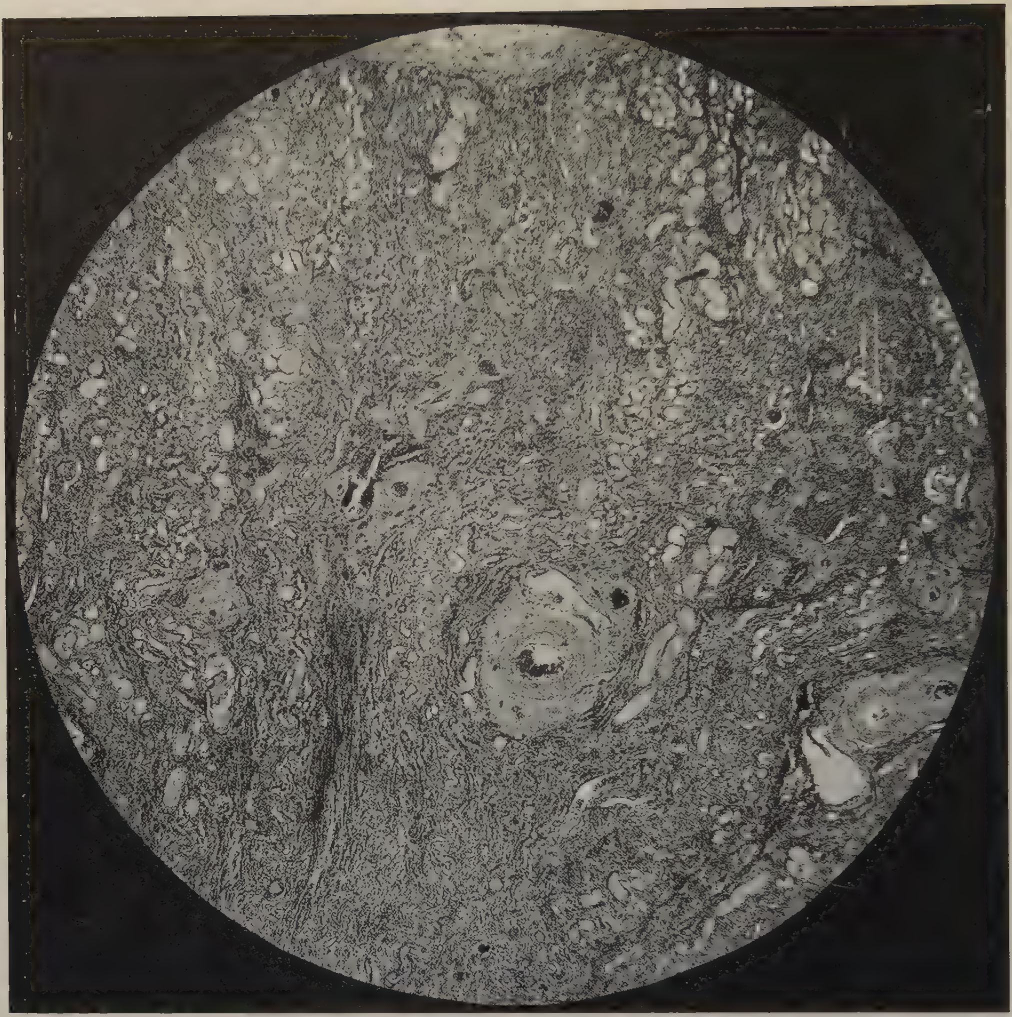

Plate XXII a

There is a very marked inflammatory proliferation of the interstitial tissue with scattered areas of round cell infiltration. It is difficult to distinguish the fibrosed glomeruli. Large areas of tubular atrophy alternate with groups of dilated tubules filled with colloid. There is an extreme sclerosis of the arteries.

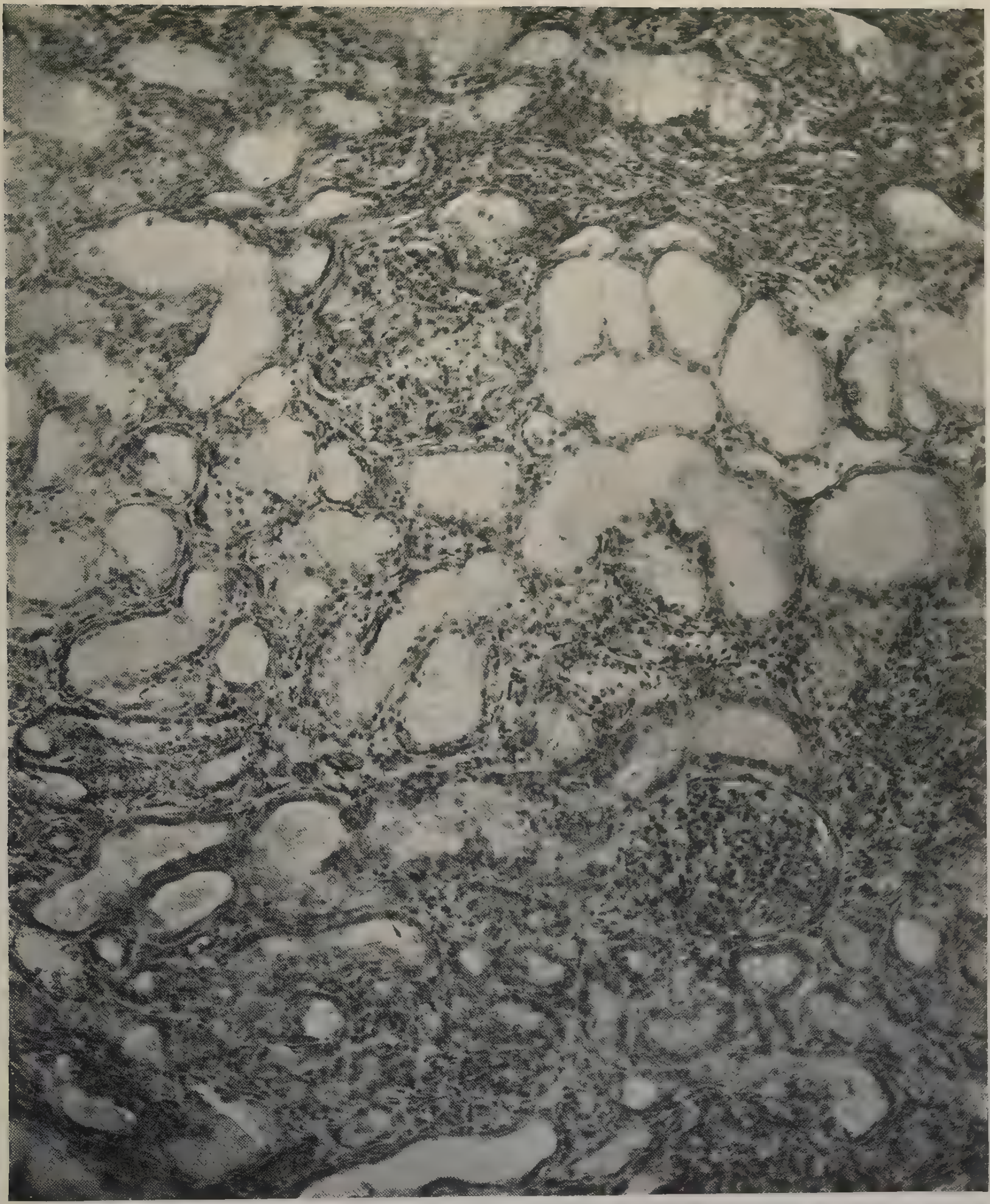

Plate XXII b

Two glomeruli are seen whose tufts are infiltrated with inflammatory cells, and whose capsular spaces are obliterated. A similar inflammatory infiltration in the interstitial tissue has caused either atrophy or dilatation of the tubules. The dilated tubules are filled with hyaline casts.

Tubules. In about one-half the cortex the convoluted tubules are compressed and atrophied and exist not as tubes but as cords of small deeply staining cells. In the regions more free of fibrosis the tubules are dilated and filled with hyaline material or casts and their epithelium is reduced to a thin layer of compressed cells. Other tubules, especially those in the deeper layers of the cortex, are more normal in their general structure. They are lined with irregular epithelial cells of regenerated type, and in many there is a parenchymatous degeneration of the epithelium. Many contain hyaline and granular casts as well as red blood cells or blood casts and in a few cases masses of polymorphonuclear leucocytes. There are many large renal failure casts in the collecting tubules.

Interstitial Tissue. There is an extensive fibrous proliferation of the connective tissue throughout the cortex. This tissue is quite cellular, and heavily infiltrated with round cells which contain a moderate number of polymorphonuclear leucocytes. This fibrosis has destroyed the entire architecture of the cortex by its effect on the tubules and glomeruli.

Arteries. The larger arcuate arteries show a marked fibrous thickening of their intima. There is a similar fibrosis of the wall of the smaller interlobular branches.

SUMMARY

The kidney shows an old but still slightly active, inflammatory involvement of glomeruli and interstitial tissue. The tubules are compressed by these processes and there is a marked sclerosis of the arteries.

CASE XXIII

Richard B. Aged seventeen.

Clinical Diagnosis. Glomerular nephritis, terminal stage.

Duration. Two years and five months. Observed during the last two years and three months.

Etiology. Scarlatinal streptococcus.

Course. On March 21, 1924, the urine was seen to be dark red in color. A week later there was a pronounced generalized edema. Evidences of a recent undiagnosed scarlet fever and of an acute hemorrhagic nephritis were found. The edema and hypertension persisted until June 1924 and for a short time during that month there was blurring of vision with edema of the discs and retinal hemorrhages, but for the next two years all these symptoms disappeared. A gradually increasing anemia remained. During the last year the blood urea concentration slowly rose, the proportion of renal failure casts increased and in June 1926 symptoms of uremia became evident. He died of uremia on July 18, 1926.

RELEVANT CLINICAL DETAILS

On March 21, 1924, the patient noted that the urine was dark red in color but it was not until March 28 that a generalized edema became obvious. A medical examination then disclosed that the urine contained albumin and considerable amounts of blood. Evidences of a previously undiagnosed scarlet fever were found. There had been an epidemic of scarlet fever at the boarding school he attended.

When first seen on May 7, 1924, there was still edema of the subcutaneous tissues and fluid in both pleural cavities. The blood pressure varied between 160 and 170 systolic and 120 and 125 diastolic. The blood urea concentration was 102 mg. per 100 c.c. The plasma showed a marked lipemia. The number of casts in twelve hours' urine was over 5,000,000, of which 2 per cent were epithelial, 4 per cent granular, 5 per cent fatty, 1 per cent waxy and 88 per cent hyaline. All these casts were sprinkled over with fat droplets. The number of red blood cells was 50,000,000 and there were 73,000,000 white blood cells and epithelial cells. The rate of protein excretion was 7.5 gm. per twelve hours. There was evidence, therefore, of a very active inflammatory and degenerative renal lesion. In June 1924 his vision became blurred and edema of the discs with hemorrhages in the retinae were found. Within two weeks, however, his eyesight was again normal and no evidences of retinitis could be found.

From June 1924 until June 1926 he remained free from obvious symptoms but there was a persistent and very slowly progressive anemia. The blood urea concentration remained within the range of normal variation until February 1925 when it was 66.6 mg. per 100 c.c. There was probably a steady increase from that time. In September 1925 renal failure casts were first seen in the urinary sediment. By April of that year the blood urea had risen to 180 mg. per 100 c.c. In June 1926 there was occasional unexplained vomiting. The anemia was then extreme. On

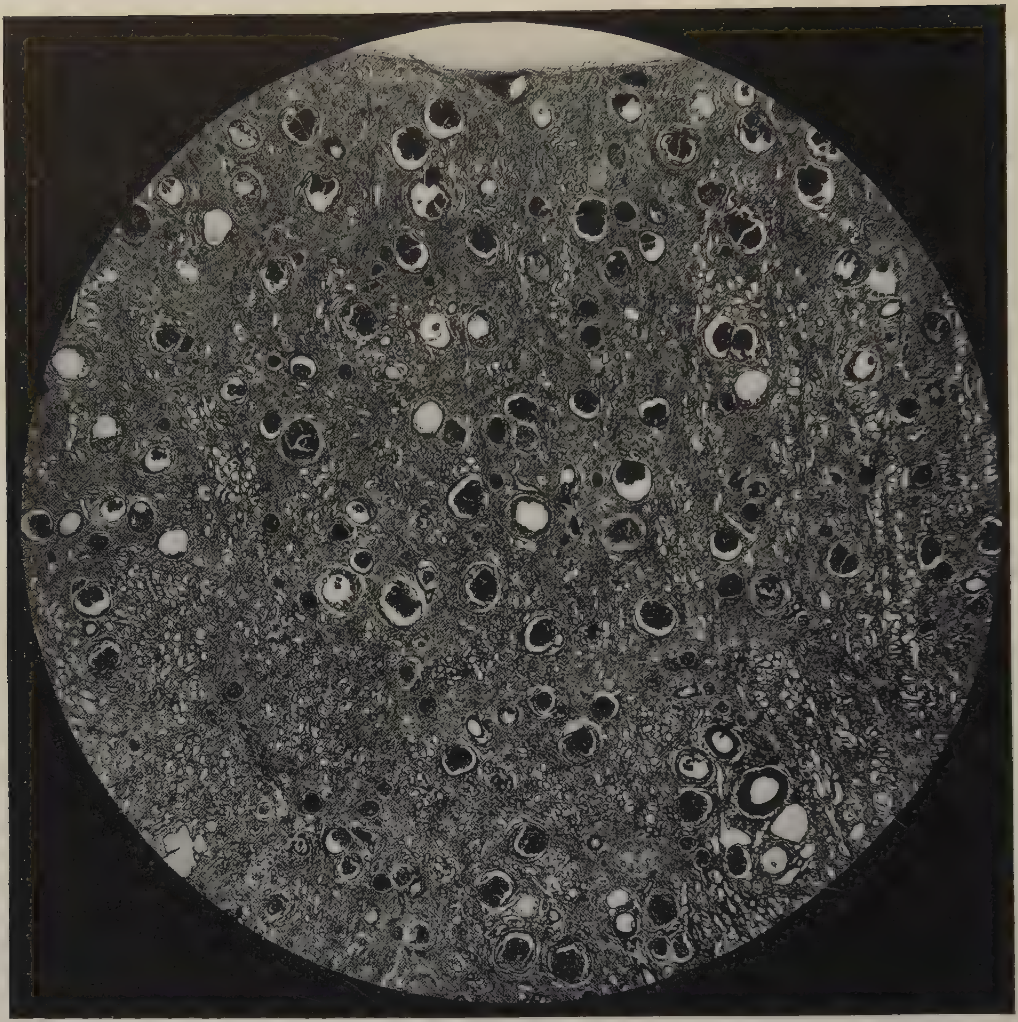

PLATE XXIII A

There is a rather even inflammatory proliferation of the connective tissue of the kidney with extensive tubular atrophy. Some of the glomeruli are large and dense as a result of the inflammatory process in them, others are greatly reduced in size by contraction. Several sclerotic arteries are evident in the lower right region of the section.

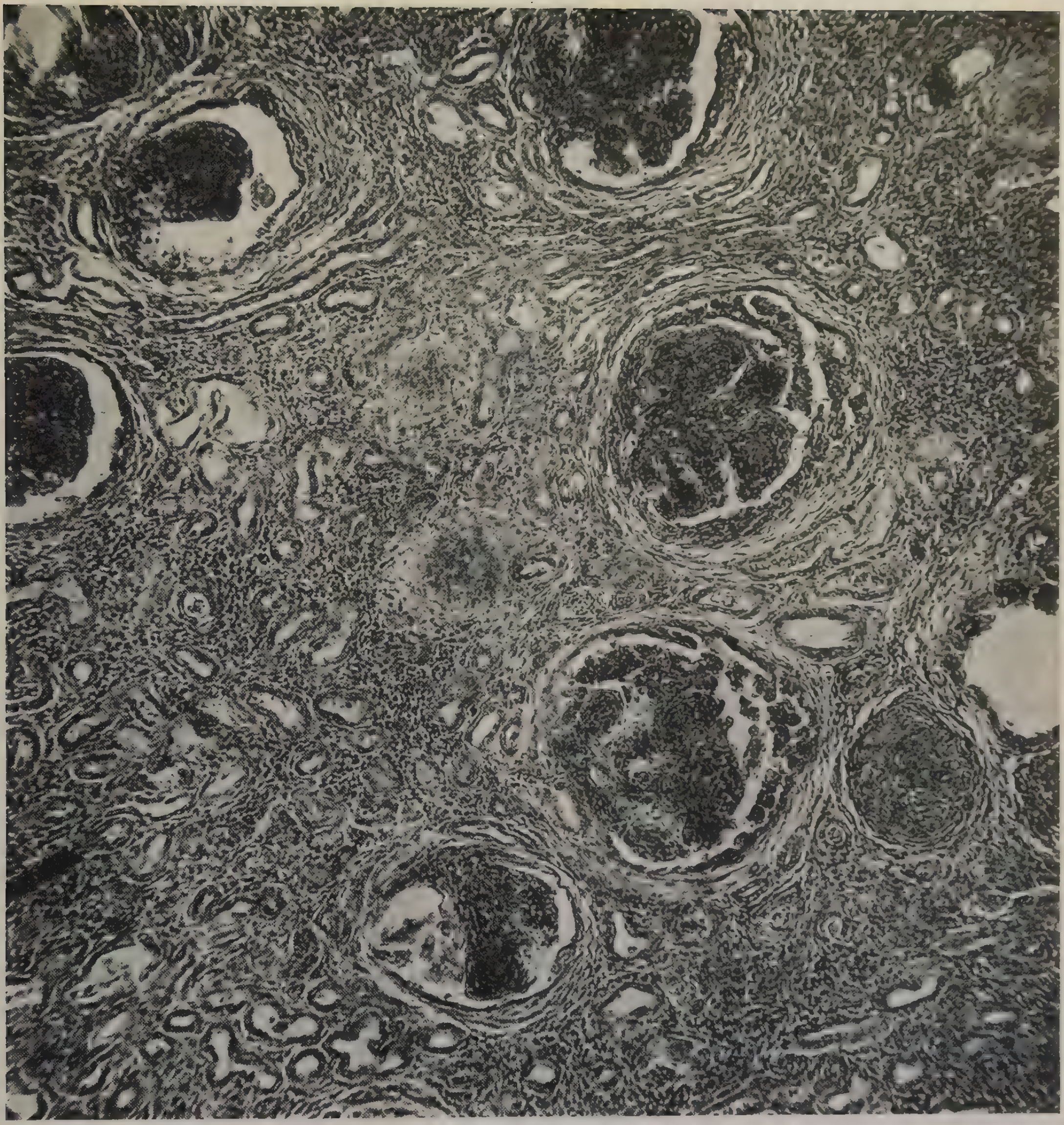

Plate XXIII b

The glomeruli are greatly enlarged by inflammatory proliferation both in the tufts and in Bowman's space. There is a very heavy leucocytic infiltration of the interstitial tissue with resulting atrophy of the tubules.

July 2, 1926, a series of transfusions was begun but they had only a very transient effect. The blood urea concentration had risen to very high levels, and all the casts were of the renal failure type. The vomiting became persistent, the patient was at times somnolent and at other times confused. He died on July 18, 1926.

Of many counts made the following are typical of the change in the transition from the active to the terminal stage.

TABLE XXVIII

Date	Casts per 12 hrs.	Renal failure casts, per cent	Red blood cells per 12 hrs.	W.B. & Ep.C. per 12 hrs.	Protein, mg. per 12 hrs.
1924	11,800,000	0	246,000,000	85,000,000	5,960
1925	655,000	+	55,000,000	16,100,000	2,130
1926	239,000	100	109,000,000	51,000,000	3,100

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained after death. They were of normal size, but the capsules were somewhat adherent. They stripped fairly easily, leaving a purplish red fine granular surface and an occasional petechial hemorrhage. The cut surface showed indistinct markings. The arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus is affected by a rather old inflammatory process. The majority are enlarged and their tufts show a marked increase in nuclei. These excess cells are fibroblasts, mononuclear leucocytes and a moderate number of polymorphonuclears and there is also a development of connective tissue fibrils. Bowman's space is filled with exudate and crescents which show more or less organization with the development of capsular adhesions. The fibrosis both in and around the tuft has transformed about one-third of the glomeruli into fibrous nodules.

Tubules. Throughout large areas of the cortex the convoluted tubules have ceased to exist as such and are represented by irregular clumps and masses of atrophic epithelial cells with no lumen. In other places they still maintain their lumens but are markedly distorted in their shape, and occasionally areas are found where they are greatly dilated and contain hyaline material. Other tubules contain granular material or hyaline and granular casts and a few groups may be found which contain red blood cells and blood casts. There are many large renal failure casts in the collecting tubules. There is only a moderate amount of cloudy swelling in the epithelium of the convoluted tubules. In the most of the tubules the epithelium though atypical in structure is well preserved.

Interstitial Tissue. Throughout the cortex there is an extensive and diffuse fibrous proliferation of the interstitial connective tissue. This, by the atrophy and dilatation of the tubules and glomeruli previously described, has produced an extreme alteration in the architecture of the kidney. In the developing inflammatory tissue is a heavy infiltration with leucocytes of both the mononuclear and polymorphonuclear type. These areas are not confined entirely to the cortex but are found extending down through the medulla.

Arteries. Both the larger arcuate arteries and the smaller interlobular branches show a moderate sclerosis.

SUMMARY

The kidney shows a diffuse inflammatory process which is quite old as judged by the proliferative changes in the interstitial tissue but still active as evidenced by the red blood cells and polymorphonuclear leucocytes in the tubules and tissues. The arteries are sclerotic.

CASE XXIV

Leila B. Aged twenty.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. One year and eleven months.

Etiology. Wound infection.

Course. In October 1927 nine days after the wound of an appendix operation had become infected a generalized edema suddenly appeared and was associated with a urine which at times was dark brown, at other times a deep red. She was told that she had an inflammation of the kidneys. When seen in May 1928 there was still some edema and hypertension. The sediment counts indicated a hemorrhagic lesion with an active degenerative process. In October 1928 a measurement of the amount of renal tissue showed that there was only 30 per cent of the usual amount of renal tissue still functioning. By July 1929 the blood urea concentration rose to definitely abnormal levels and her eyesight became dim from retinitis. During August she became uremic and died while unconscious on August 31, 1929.

RELEVANT CLINICAL DETAILS

Examinations carried out between January and June 1927 showed that the urine was normal and that there was no hypertension. During August and September 1927 she suffered at times from pain in the lower part of the abdomen associated with some increase in the frequency of urination. On September 14, 1927 her tonsils were removed. Three days later there was a considerable hemorrhage from the wound. On September 28, after a severe attack of abdominal pain the operation of appendectomy was performed. Her throat which was still sore became much worse and she expectorated pus for some weeks afterwards. The operation wound became infected and did not heal for a long time.

On October 7, 1927, nine days after the appendectomy, an edema suddenly developed, which involved the whole body, including her hands and feet, and almost completely closed her eyes. At the same time it was noted that the urine was alternately dark brown or red like blood. She was seen by a doctor who told her that her kidneys were inflamed. The edema gradually decreased and in a month was gone. The obvious hematuria lasted for about five weeks. From the onset on October 7, 1927 until she was first seen in May 1928 she stayed in bed and took a calorically insufficient diet, at first of milk, and later milk and vegetables. There was one period when the edema returned for a few weeks during a severe cold in the head but the urine did not become red or brown. She was weak and lost part of the small quantities of food she took by vomiting. On May 5, 1928 although there was a slight edema present her weight was only 95 lbs., a decrease of 24 per cent below her weight before the illness.

Physical examination failed to reveal any evidence of cardiac enlargement or of arterial disease though the blood pressure was at the time 160 systolic and 110 diastolic. There was marked emaciation and slight edema of the legs. There was no obvious anemia. A blood count showed 4,000,000 red blood cells.

A concentration test had a volume of 148 c.c. per twelve hours and a specific gravity of 1.035. There were 770,000 casts per twelve hours. The differential count showed no blood casts, 2 per cent epithelial, 4 per cent granular, 4 per cent fatty, 2 per cent waxy and 88 per cent hyaline casts studded with fat droplets. The number of red blood cells was 13,000,000 per twelve hours and nearly the same rate was found for white blood cells and epithelial cells. The rate of protein excretion was 3860 mg. per twelve hours. The blood urea concentration was 27 mg. per 100 c.c. Two months later with a blood urea concentration, measured before the administration of urea, of only 25 mg. per 100 c.c. the quantity of functioning renal tissue was found to be only 30 per cent of the normal. The predominant features of this sediment were the evidences of an intense degenerative lesion, but the very definitely abnormal number of red blood cells, even in the absence of blood casts, was enough to exclude any pure degeneration and to bring the diagnosis into consonance with the quite clear and unequivocal history.

The subsequent history of the sediment changes are shown in Table XXIX.

Throughout 1928 the signs of a fatty degeneration of the kidney persisted. In 1929 the fat droplets disappeared and by August 13 when the blood urea concentration had risen to 164 mg. per 100 c.c. some renal failure casts were found. The examinations made when uremia was clinically evident revealed, as not infrequently happens when the volume of urine is over 1000 c.c. per twelve hours, no casts, only a marked increase in epithelial cells.

During the fifteen months of observation before her death there were four occasions when pharyngitis, with fever lasting for three or four days, was accompanied by a slight return of edema but in the intervals she was well and able to work. There was no progressive anemia. The blood pressure tended on the whole to rise but there were no symptoms of circulatory difficulty. On July 20, 1929 however there was a sudden dimness of vision due to the laying down of exudate in the macular regions of both eyes. The systolic pressure was now always over 200 and the diastolic pressure over 140. In the early part of August the patient was in a definitely toxic state and suffering often from severe headaches. Soon afterwards pericarditis developed. The patient became stuporous, later deeply unconscious and died on August 31, 1929.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a local arteriosclerosis and a healed apical pulmonary tuberculosis. As terminal infections there were present a serofibrinous pericarditis, an acute stomatitis and a bronchopneumonia. The kidneys were similarly reduced in size, measuring 10 × 5 × 3 cm. The capsule was somewhat adherent, but stripped fairly easily, leaving a granular reddish purple surface. The cut surface showed a reduction of the cortex and a moderate thickening of the renal arteries.

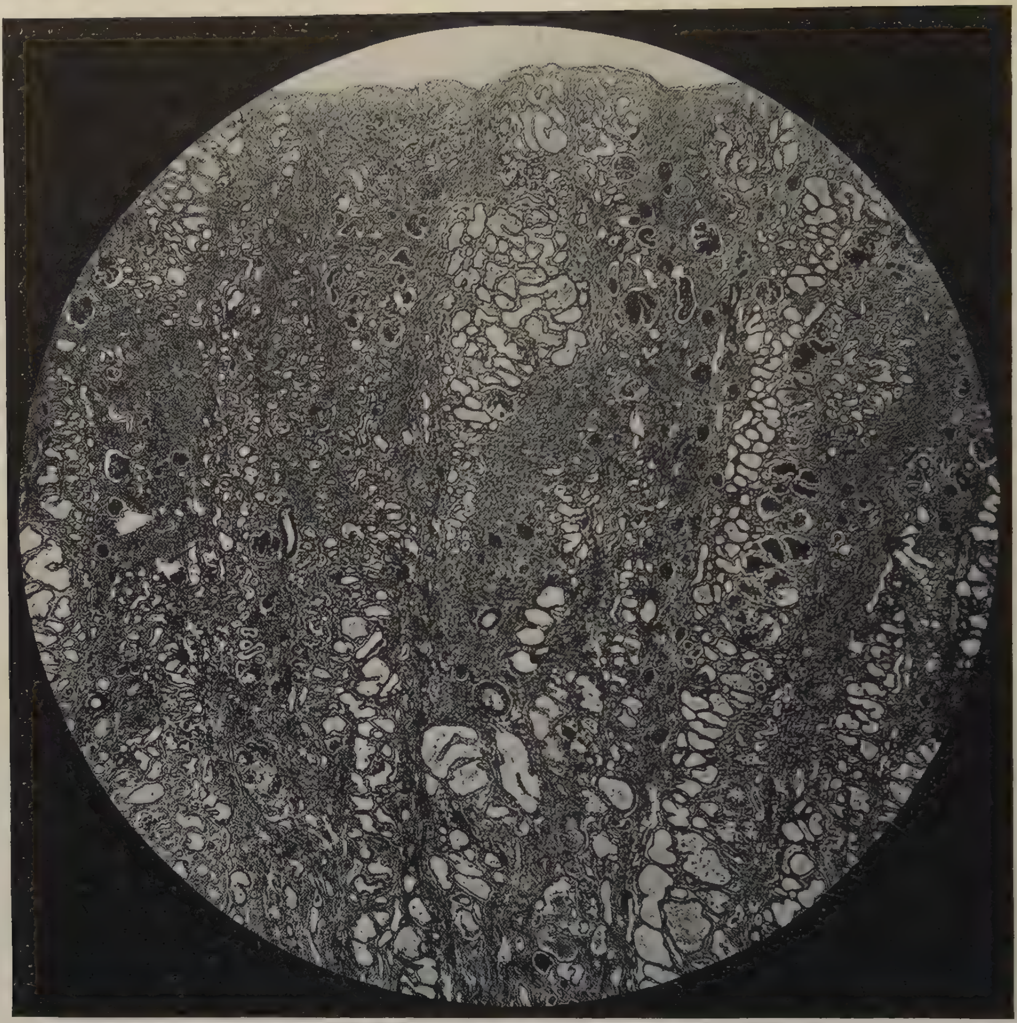

Plate XXIV a

A majority of the glomeruli have disappeared as a result of the proliferative inflammatory lesions. Others may still be made out in various stages of the inflammatory process. The architecture of the cortex is markedly altered by collapsed and dilated tubules which alternate throughout the section. The latter are filled with various sorts of material. The granular surface of the kidney is apparent.

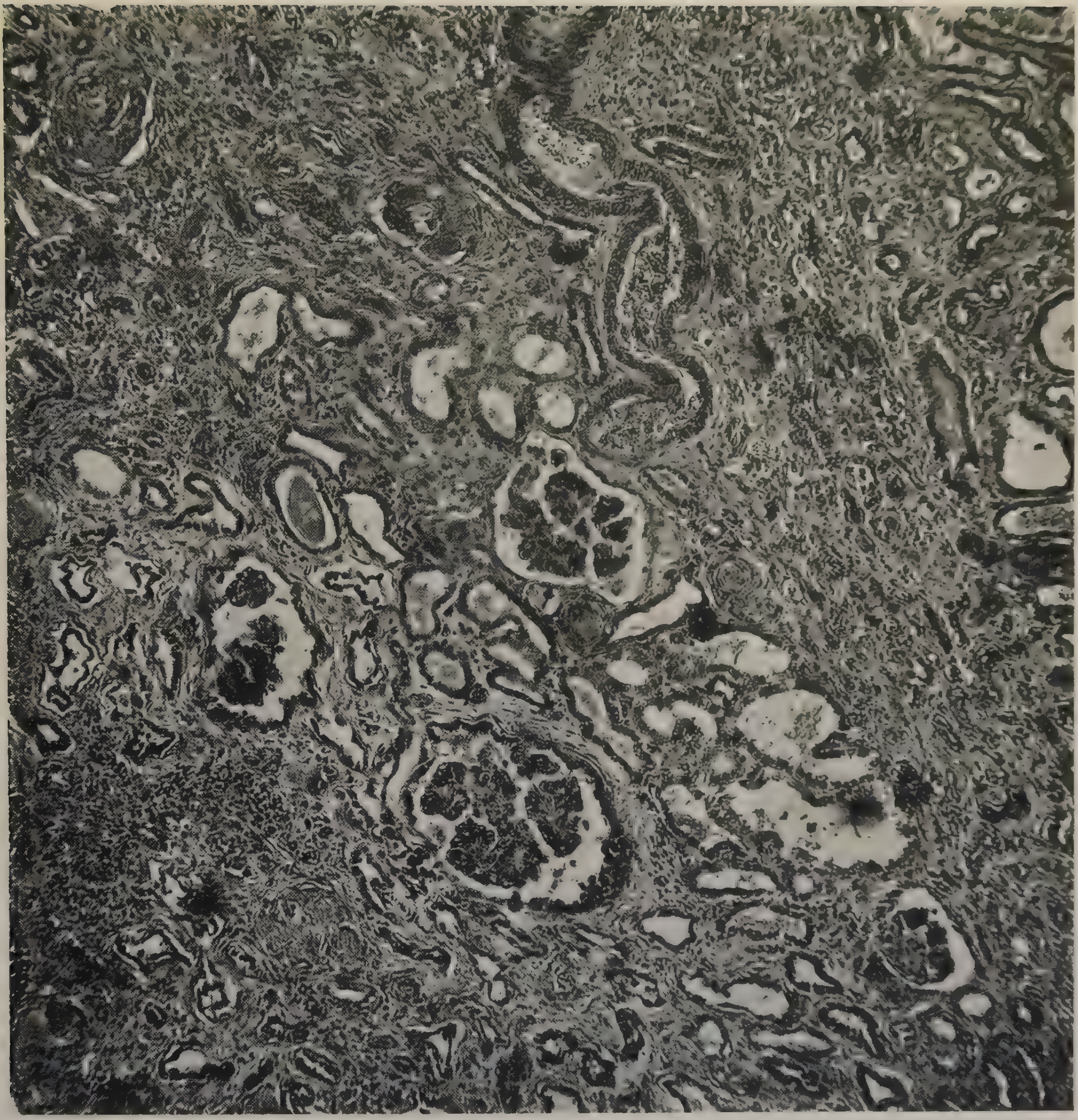

Plate XXIV b

Four glomeruli show the active inflammatory processes in their tufts. To the left of the artery, which is definitely thickened, the hyaline remains of two other glomeruli are seen. The proliferating interstitial tissue is heavily infiltrated with leucocytes. The epithelium of the distorted tubules shows severe degenerative changes. (Cf. Plate xciv.)

Table XXIX

Date	No. of casts 12 hrs.	Differential cast count (per cent)							R.B.C. 12 hrs.	W. & Ep. 12 hrs.	Pro-tein mg. 12 hrs.	Vol.	Sp. gr.	Blood urea	Ratio per cent of normal	Blood press.	
		Bl.	Ep.	Gr.	Fa.	W.	Hy.	Renal fail.								Sys.	Dias.
May 22, 1928..	770,000	..	2	4	4	2	88	..	13,700,000	13,000,000	3,860	148	1.035	27	..	140	100
June 9, 1928...	620,000	..	..	3	2	..	95	..	3,500,000	5,700,000	4,425	192	1.028				
June 14, 1928..	148,000	..	..	..	..	..	..	..	9,000,000	....	4,274	532	1.019	...	..	160	120
July 19, 1928..	129,000	..	..	..	..	..	..	..	2,560,000	6,400,000	3,243	213	1.025	47	..	140	105
Oct. 23, 1928..	....	..	..	..	..	..	..	..	....	....	.....	.....	.....	25	30	165	120
Nov. 15, 1928..	140,000	..	..	..	..	..	100	..	3,360,000	4,500,000	3,885	348	1.022	...	..	170	130
Dec. 15, 1928..	1,520,000	..	..	..	..	..	100	..	4,560,000	....	3,900	475	1.016	...	..	175	125
Feb. 2, 1929...	93,600	..	..	..	..	..	100	..	4,482,000	9,000,000	4,530	936	1.016	...	..	170	130
Mar. 30, 1929..	....	..	..	..	..	..	..	..	....	....	.....	.....	.....	38	..	175	
July 20, 1929..	0	..	..	..	..	..	..	..	7,200,000	1,750,000	5,945	500	1.018	69	..	210	170
Aug. 13, 1929..	172,000	..	6	30	4	..	56	4	....	....	.....	303	1.010	164	..	220	145
Aug. 28, 1929..	....	..	..	..	..	..	...	..	....	....	.....	.....	.....	353			
Aug. 30, 1929..	0	..	..	..	..	..	...	..	6,200,000	18,000,000	5,020	1,035	1.013	450	..	200	145

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli show varying stages of a chronic inflammatory process. Some are enlarged, heavily infiltrated with leucocytes, a few of which are polymorphonuclears, and are filled with fibrous connective tissue. Capsular adhesions are frequent, and where Bowman's space is preserved it contains granular material, leucocytes and occasionally a definite capsular crescent. Other glomeruli are decreased in size, evidently from the retraction of fibrous connective tissue and about one-third the total number are reduced to hyaline nodules.

Tubules. In the areas of connective tissue proliferation throughout the cortex the tubules are compressed and distorted and their epithelium atrophied. Between such areas however the tubules are either greatly dilated, their epithelium flattened by the colloid-like material which fills their lumen, or the epithelium is hypertrophied. These latter tubules show a marked cloudy swelling and some necrosis with degeneration of their epithelium. The tubules contain granular material, all types of casts including blood casts and, in the collecting tubules, renal failure casts.

Interstitial Tissue. There is a marked irregular development of fibrous but still cellular connective tissue throughout the cortex. There is an equally irregular infiltration of this tissue with leucocytes, and where the denser masses of it reach the free surface of the cortex retracted scars are formed.

Arteries. The arcuate arteries show an irregularly distributed fibrous thickening of their intima. In some the process is quite marked while in others the intima is normal. The small interlobular branches also show the same irregularity in the fibrous thickening of their walls.

SUMMARY

The glomeruli and interstitial tissue show old but still active inflammatory changes. There are active degenerative processes in the epithelium of the tubules. The arteries show a moderate sclerosis. Renal failure casts are present.

CASE XXV

John A. B. Aged twenty-six.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Three years or more. Observed during the last twenty-four days.

Etiology. No information.

Course. The initial stage passed unnoticed. The presence of a small amount of albumin and of some casts in the urine was noted in September 1922 but at that time no other abnormalities were found. He remained without symptoms until June 1925 when he noted general weakness and lassitude. In October 1925 there was a sudden blurring of vision. The urine at that time remained constantly dilute.

RELEVANT CLINICAL DETAILS

In 1905 he had scarlet fever but no complications were noted. In 1910 there was a severe and long-continued iridocyclitis and at that time a small amount of albumin was found in the urine, but in 1923 he had entirely recovered and repeated urinary examinations gave negative results. In 1914 he had an attack of follicular tonsillitis but between 1917 and 1921 several insurance and army examinations failed to disclose any albumin in the urine. However, in September 1922 a small amount of albumin and some casts were found on a routine urine examination, but his health was excellent and no other abnormalities could be discovered. It seems probable that he was then in the latent stage of the disease.

He remained quite well until June 1925 when he consulted his family physician because his work was tiring him. His doctor was surprised to find a considerable quantity of albumin in the urine. He was kept in bed on a milk diet but lost weight and strength and in October there was a sudden blurring of vision.

He was first seen on October 29. There was an exudative retinitis with fresh hemorrhages. The heart was enlarged to the left, the blood pressure was 230 systolic and 148 diastolic. A concentration test gave a volume of 859 c.c. per twelve hours with a specific gravity of 1.012. The rate of protein excretion was 2530 mg. per twelve hours. The casts were all of the renal failure type. The number in twelve hours' urine varied between 132,000 and 206,000. Two specimens were so dilute that no casts of any sort were found, but in one of seven examinations a few hyaline casts could still be seen among many of the renal failure type. The number of red blood cells was very variable. One specimen contained as many as 127,000,000 per twelve hours, while in another there were only 2,860,000. The number of white blood cells and of epithelial cells varied between 14,500,000 and 1,140,000. The blood urea concentration was 105 mg. per 100 c.c. but a few days later it had risen to 164 mg. and on the thirteenth day after admission the concentration was 204 mg. per 100 c.c. Although weaker and now almost completely blind he was not uncomfortable and was able to take food and to talk with his friends. On the eighteenth day, however, he had a severe headache, vomited his food and complained of itching of the skin. Thereafter he took very little to eat, became more and more somnolent and died on the twenty-fourth day after admission.

PATHOLOGICAL OBSERVATIONS

The kidneys and a portion of the liver and the spleen only were obtained at autopsy. The kidneys were about normal in size, measuring 10 × 5.5 × 4 cm. The capsules stripped fairly easily, leaving a somewhat granular surface of deep purple color on which were scattered lighter colored areas 1 to 3 mm. in diameter. On the cut surface the cortex was definitely narrowed, measuring about 3 mm. in breadth, and the markings were indistinct. The pyramids were congested. The renal arteries were considerably thickened.

MICROSCOPICAL EXAMINATION

Sections of liver showed a marked congestion of the capillaries with beginning necrosis of the liver cells in the centers of the lobules.

Sections of spleen showed an extreme congestion and a marked hyaline degeneration of the arteries.

KIDNEYS. *Glomeruli.* Practically all the glomeruli are smaller than normal, there is an increase in the intracapillary connective tissue and also a marked increase of nuclei within the tuft. Many of the latter are those of polymorphonuclear leucocytes and of lymphocytes. The capsular space in the majority of the glomeruli is free, though some contain granular material, and occasionally a typical glomerular crescent of organized exudate and leucocytes is found.

Tubules. Associated with a diffuse fibrosis in the cortex is a marked irregularity of the convoluted tubules. In some regions they are as large as normal, or even larger, with thick well-developed epithelium, while in others, where the fibrosis is most marked, they exist as compressed cords of atrophic cells. In all there are various degrees of parenchymatous degeneration from cloudy swelling to a frank necrosis. There is also considerable evidence of regeneration, as indicated by the occurrence of an excessive number of large nuclei and cells arranged in irregular masses and layers. There are many casts of all sorts in the lumens of the tubules; occasionally red blood cells or blood casts are found.

The broad ascending limbs of Henle's loop show the same changes. The collecting tubules of the medulla are normal except that many broad renal failure casts are present.

Interstitial Tissue. There is a marked increase in connective tissue throughout the cortex, to such a degree in fact that it has compressed the tubules as already described. Scattered through this tissue are many leucocytes, principally lymphocytes but also polymorphonuclears.

Arteries. There is a very marked fibrous thickening of the intima of the arteries. The smaller branches are particularly affected; some of these in the cortex are almost obliterated.

SUMMARY

The kidneys show an old intracapillary glomerulitis associated with parenchymatous degeneration of the epithelium, interstitial proliferation and intimal thickening in the arteries. Many renal failure casts are present.

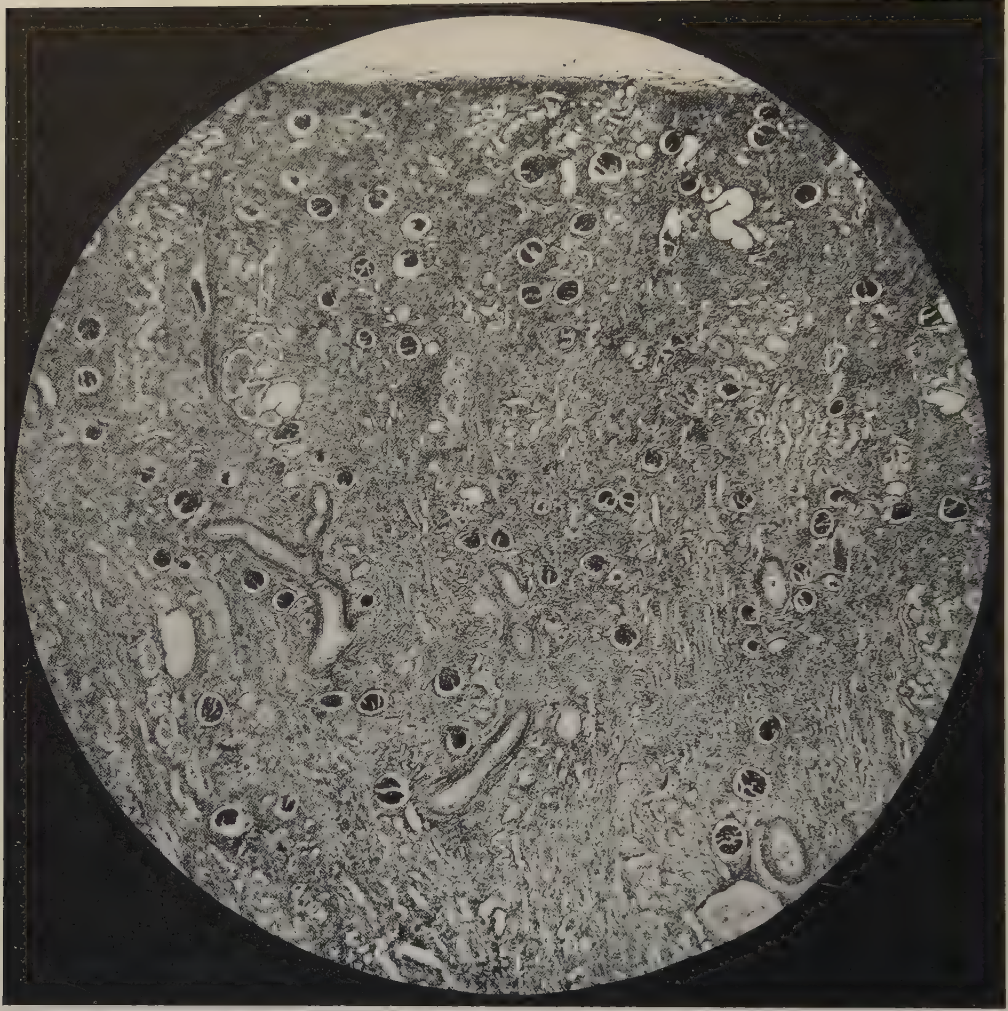

Plate XXV a

There is a marked cellular and fibrous inflammatory proliferation of the interstitial tissue with accompanying tubular destruction or cystic dilatation. Many glomeruli are present but all are in varying stages of inflammatory destruction. The branches of interlobular arteries to the cortex show a marked sclerosis.

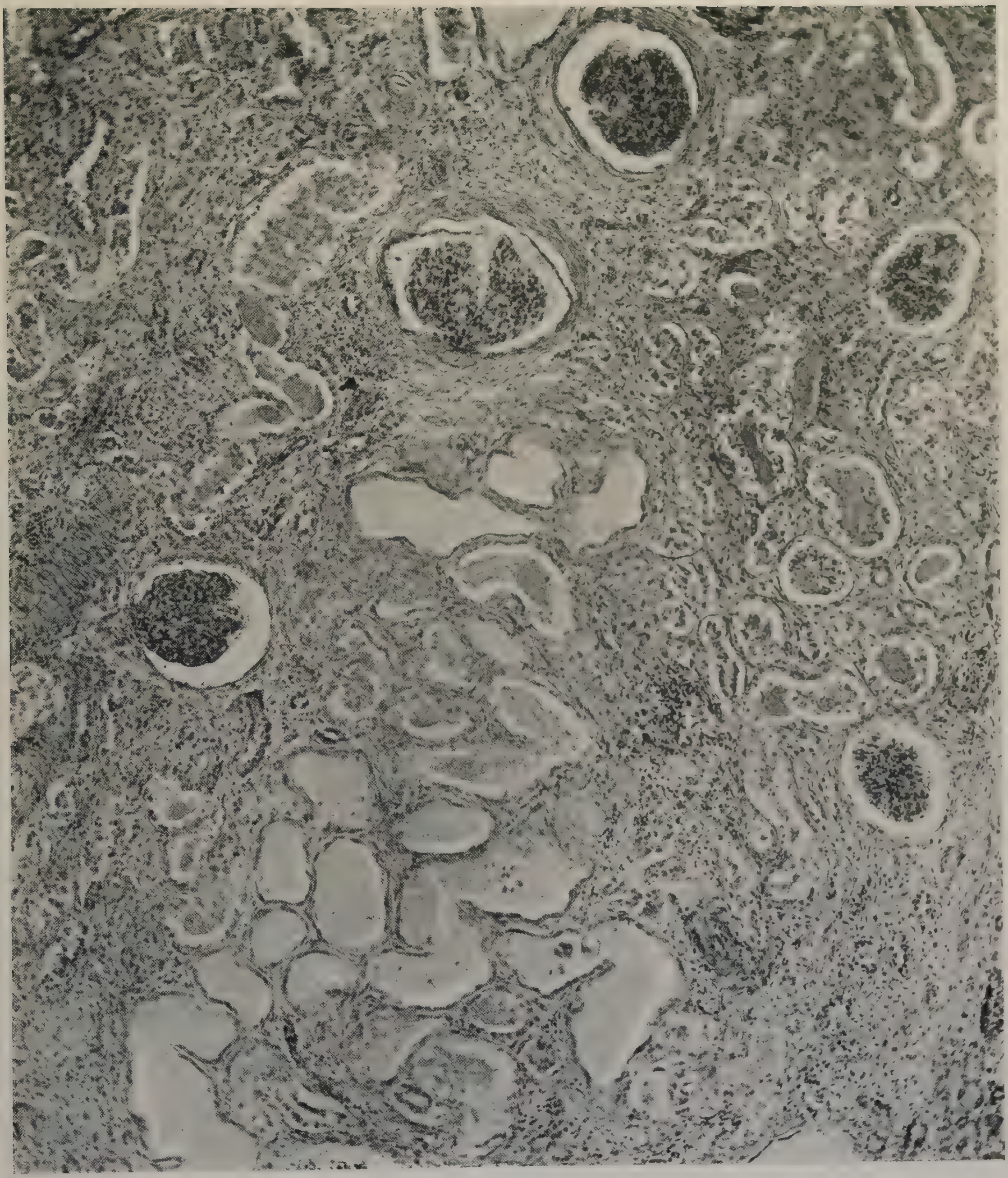

PLATE XXV B

The shrunken fibrous glomeruli are well shown. There is a marked irregular fibrosis of the interstitial tissue with considerable leucocytic infiltration. The tubules show the usual effects of compression or dilatation.

CASE XXVI

John B. Aged fifty-one.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Eight years. Observed for three weeks before death.

Etiology. Unknown.

Course. Five weeks before death the patient's friends noted that his face was swollen and in the next few days his legs became markedly edematous. He noticed the dark color of his urine and recalled that eight years before the same symptoms had been observed over a period of about two months. The urine was smoky with blood and contained many renal failure casts. The blood urea concentration rose steadily to 448 mg. per 100 c.c. just before death.

RELEVANT CLINICAL DETAILS

The patient was a laborer and not very observant, but he remembered that eight years ago his face and legs had been swollen, and that his urine had had a peculiar dark color. He thought the swelling had remained for about two months, but he had not consulted a doctor and no urine examination had been made. When five weeks before his death his friends called his attention to the swelling of his face, he looked at his urine and saw that again it had the "dark" appearance which he had previously observed. During the few years preceding his last illness he had been troubled with occasional severe headaches and had had to rise two or three times every night to void urine, but he had been able to work fairly steadily and had not thought that he had any serious chronic illness. Soon after the swelling appeared in his face he lost his appetite and vomited several times immediately after eating, though he was not nauseated. The swelling spread downwards and became pronounced in his legs. He noticed also that his abdomen was becoming more and more distended. There was dyspnea on exertion but it was not a marked or early symptom.

When he was admitted to the hospital two weeks after the onset of the swelling he had marked edema of both lower extremities and a considerable amount of free fluid in the abdominal cavity. The heart did not appear to be enlarged, though there was very definite left ventricular preponderance. The systolic pressure was 130 and the diastolic 90. The retinal arteries were small and tortuous. There was a slight secondary anemia. The blood urea concentration was 359 mg. per 100 c.c. After only partial abstention from fluids during the day the twelve hours' night urine had a volume of 660 c.c. and a specific gravity of 1.015. The specimen contained 5870 mg. of protein. There were 642,000 casts in twelve hours, 12 per cent of these were hyaline, 4 per cent waxy, and 84 per cent were renal failure casts. The number of red blood cells was estimated as about 970,000,000 and the white blood cells and epithelial cells as about 89,000,000. There was therefore a very active renal lesion although the terminal stage had been reached.

The blood urea concentration steadily rose, the patient became stuporous and died in coma twenty days after admission.

PATHOLOGICAL OBSERVATIONS

Autopsy showed a moderate edema of the face and legs. The heart was not enlarged. The aorta and coronary arteries showed a few yellow spots and there was an extensive terminal bronchopneumonia with involvement of both lungs.

The left kidney was of normal size, measuring 12 × 6 cm. The capsule stripped easily, leaving a pinkish yellow fine granular surface in which were a rather large number of small round hemorrhages. The cut surface showed some mottling of the cortex, but was otherwise normal. The renal artery was normal. The right kidney was the same as the left.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are involved by a subacute glomerulitis. The lesion is of both the intracapillary and extracapillary type with a resulting almost complete fibrosis and collapse of the majority of the glomeruli. In the fibrous tufts as well as in the organized exudate in Bowman's space there are many leucocytes, a considerable proportion of which are of the polymorphonuclear type and occasionally the space is found full of freshly shed red blood cells.

Tubules. There is a very marked irregularity of the convoluted tubules in the cortex. Some are dilated, but the majority are compressed and collapsed. The epithelium is also very irregular and of the atypical regenerated type. In some tubules the lumen is almost completely obliterated by the proliferated cells.

Casts of all sorts are found in both the convoluted and straight tubules. In the former there are epithelial debris, leucocytes including polymorphonuclears and red blood cells in all stages of disintegration. In the straight tubules well-formed casts are present, including blood casts and large renal failure casts in the larger collecting tubules.

Interstitial Tissue. There is a marked increase in the amount of interstitial tissue due to a proliferation of the fibrous connective tissue combined with a leucocytic infiltration. This increase has produced the distortion of the tubules already described.

Arteries. There is a moderate fibrous thickening of the intima of the arteries.

SUMMARY

The kidney shows a late but still active stage of an intracapillary and extracapillary glomerulitis associated with extensive interstitial proliferation and moderate epithelial lesions.

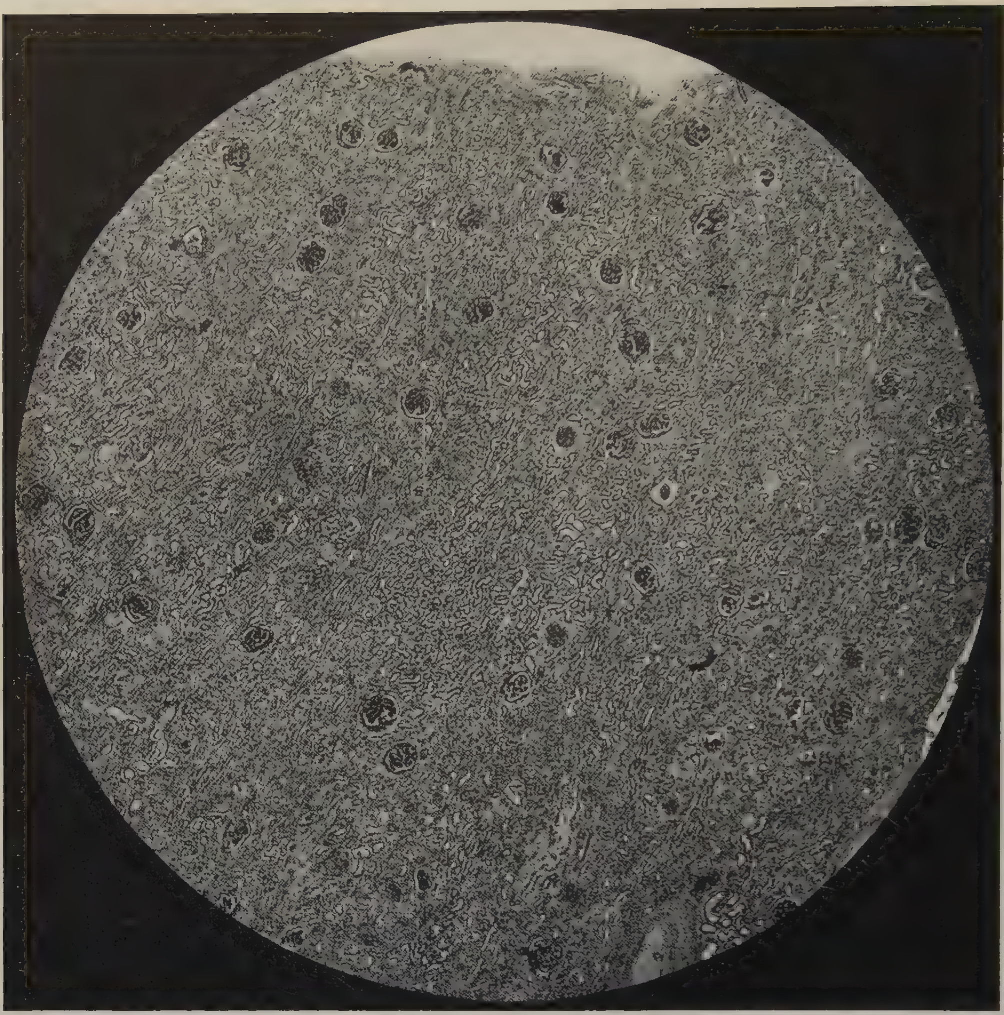

PLATE XXVI A

There is a very even fibrosis of the interstitial tissue and as a result the tubules are everywhere compressed and atrophied. The glomeruli are all involved, showing either enlargement or contraction depending on the stage of the inflammatory process.

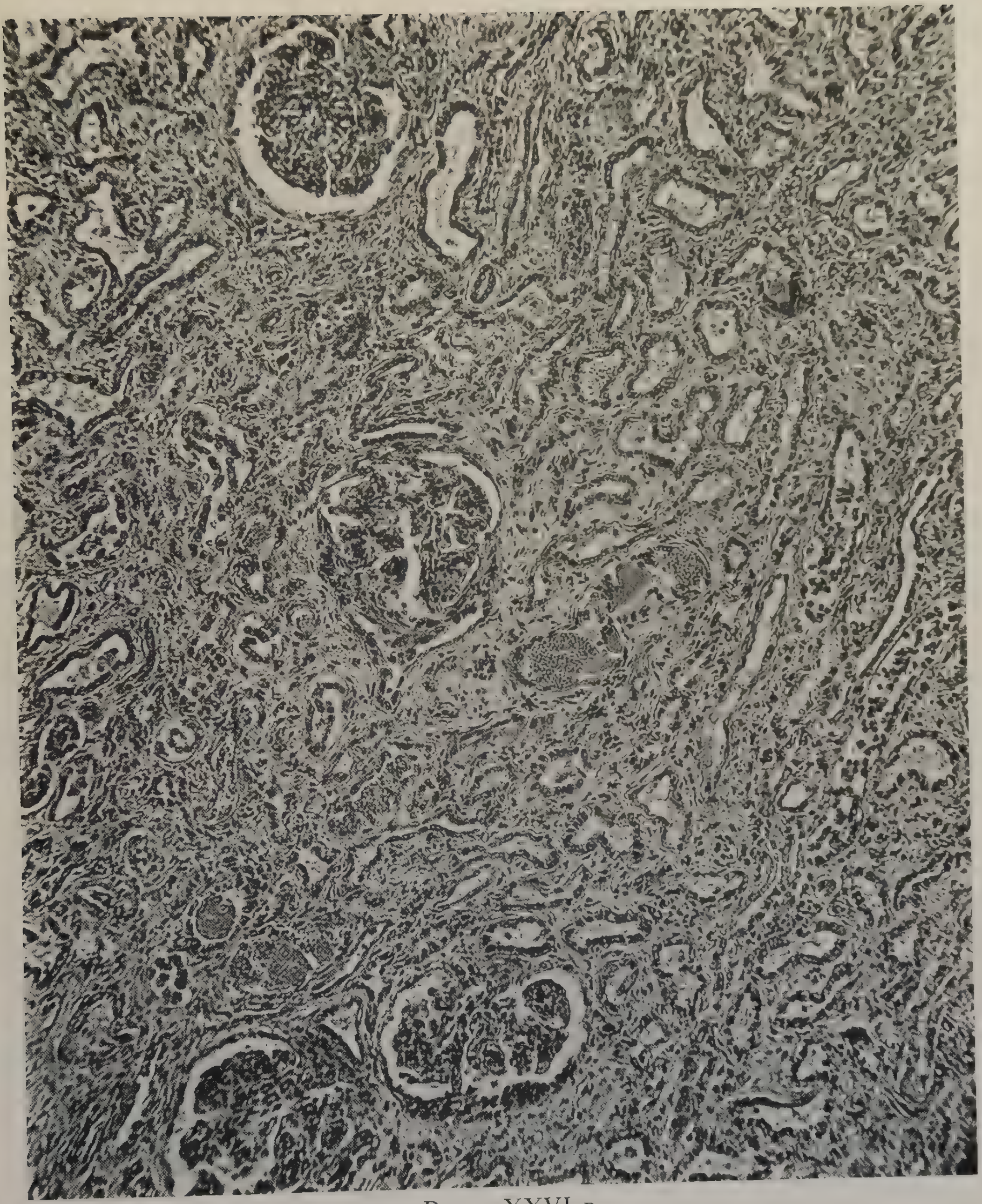

Plate XXVI b

There is a cellular proliferation of the interstitial tissue with a marked irregular distortion of the tubules. The glomerular tufts are fibrous and Bowman's space is obliterated by adhesions. (Cf. Plate xcii.)

CASE XXVII

Nicholas C. Aged twenty-six.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Two and a half years. Observed during the last twelve days.

Etiology. No information.

Course. The initial stage probably occurred in the autumn of 1921, though there is no history of edema. During 1922 and 1923 the patient suffered from an increasing asthenia with frequent headaches which for several months before his death were very severe and associated with vomiting. He was first seen in the terminal stage with a typical uremic urinary sediment. He died twelve days after admission to the hospital with a blood urea concentration of 601 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

Unfortunately this patient was so ill when he was first seen that it was not possible to obtain a history in as much detail as was desired. He was quite clear, however, in dating the gradual development of his condition from an illness which he incurred while in Java about October 1921. It began apparently with a transient fever which he thought was malarial. The doctor, however, told him that his urine contained albumin and persuaded him to live for a month on nothing but milk and rice. He had no distinct recollection of any other symptoms and against his doctor's advice he returned to an ordinary diet. Since then, he stated, he had never felt quite well. There was always a sense of weakness and though he was able to continue his clerical work he was easily tired. Soon also he began to suffer from headaches and the weakness seemed to increase. At no time was there any edema. He never consulted a doctor and knew nothing about the condition of his urine.

During 1922 and 1923 he was off work on several occasions because of the severity of the headaches, which were now associated with vomiting and a sense of extreme weakness.

About October 1923 he noted that his eyesight was blurred. The headaches from that time onwards were much more frequent and severe, and his sight seemed to be growing more and more dim.

On February 18, 1924, he experienced sharp pain in the upper abdomen and had an unusually intense headache with prolonged vomiting. He took very little to eat from that time until his admission to the hospital ten days later.

On February 28, 1924, when he was first seen, he was pale and showed signs of loss of weight. There was no trace of edema. The heart did not give any evidence of enlargement on percussion. The blood pressure was 220 systolic and 140 diastolic. There was an extensive neuroretinitis, with edema, exudate and fresh hemorrhages. Tenderness and spasticity of the upper abdominal muscles were noted especially marked on the right side. The hemoglobin concentration was estimated as 68 per cent.

On March 4 a concentration test gave a volume of only 154 c.c. with a specific gravity of 1.013. The rate of protein excretion was 920 mg. per twelve hours. There were 5,900,000 red blood cells and 2,400,000 white blood and epithelial cells in the twelve hours' urine. The number of casts was 580,000. They were all of the renal failure type and many of them were very broad.

The blood urea concentration on the day of admission was 248 mg. per 100 c.c. Five days later it had risen to 317 mg., on the ninth day it was 477 mg. and on the twelth day after admission shortly before his death the level of 601 mg. per 100 c.c. was attained.

The patient suffered from vomiting and hiccup for the first few days but thereafter was drowsy. There was a tonic rigidity which continued for twenty minutes on the seventh day, but there was no recurrence. Thereafter, for the most part, he was unconscious even though restless. During the last three days bleeding from the nose and gums and evidences of colitis were noted.

PATHOLOGICAL OBSERVATIONS

At autopsy there were found as terminal infections an acute fibrinous pericarditis, a colitis and bronchopneumonia. There was also present a secondary anemia with hematogenous pigmentation of spleen and liver, a general arteriosclerosis of moderate degree and cardiac hypertrophy.

The kidneys were small and of equal size, measuring 1.5 × 5 × 3 cm. The capsules stripped fairly easily, leaving a slightly granular greyish pink surface in which were some punctiform hemorrhages. The cut surface showed a definite reduction in the breadth of the cortex and indistinct markings. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli show an old inflammatory process. A few, about one-sixth of those examined, still maintain their normal size but their tufts are heavily infiltrated with mononuclear leucocytes and a few polymorphonuclears and show considerable proliferation of fibrous connective tissue. Adhesions have obliterated Bowman's space in the majority; in a few a small portion of the space is still patent. The remaining glomeruli have been transformed by the inflammatory process to fibrous masses, some so small as to be recognized as such with difficulty.

Tubules. In large areas of the cortex the tubules can be seen only as irregular cross sections of solid cords of atrophic atypical epithelial cells. Others, the great majority, show a rudimentary lumen. In some places, which are less densely scarred by the developing connective tissue, the tubules are greatly dilated and contain hyaline or colloid-like material. Their epithelium is compressed to a thin endothelial-like layer. In other tubules, whose epithelium still remotely resembles the normal appearance, there is cloudy swelling of the more severe type with necrosis and desquamation. Polymorphonuclear leucocytes are present in the debris that fills the lumen of these tubules. Other tubules, seen as groups in cross section, contain

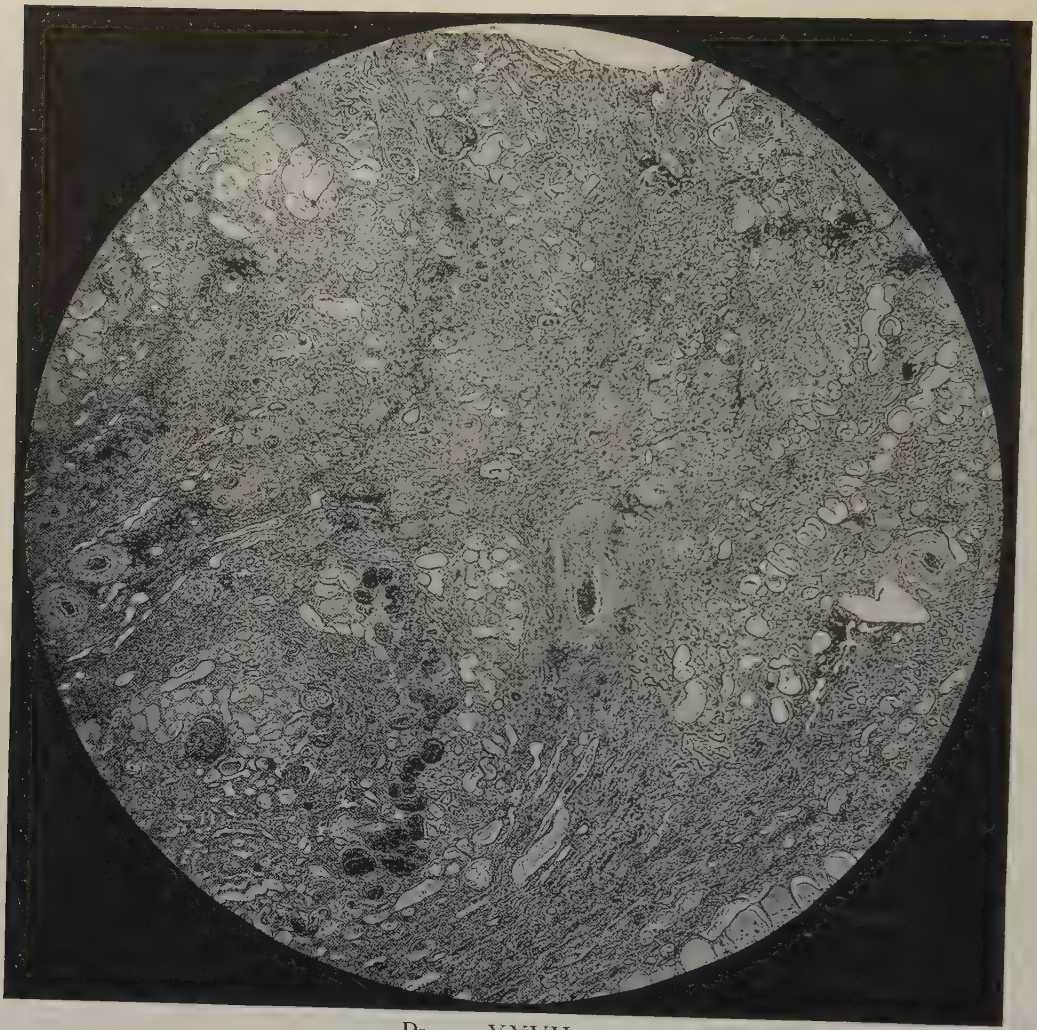

Plate XXVII a

There is a marked irregular fibrous thickening of the connective tissue. As a result the tubules are either completely collapsed or greatly dilated. It is difficult to make out even a single glomerulus in the section as they are small and fibrous and therefore blend with the inflammatory connective tissue of the framework of the kidney. Several arteries show a marked sclerosis.

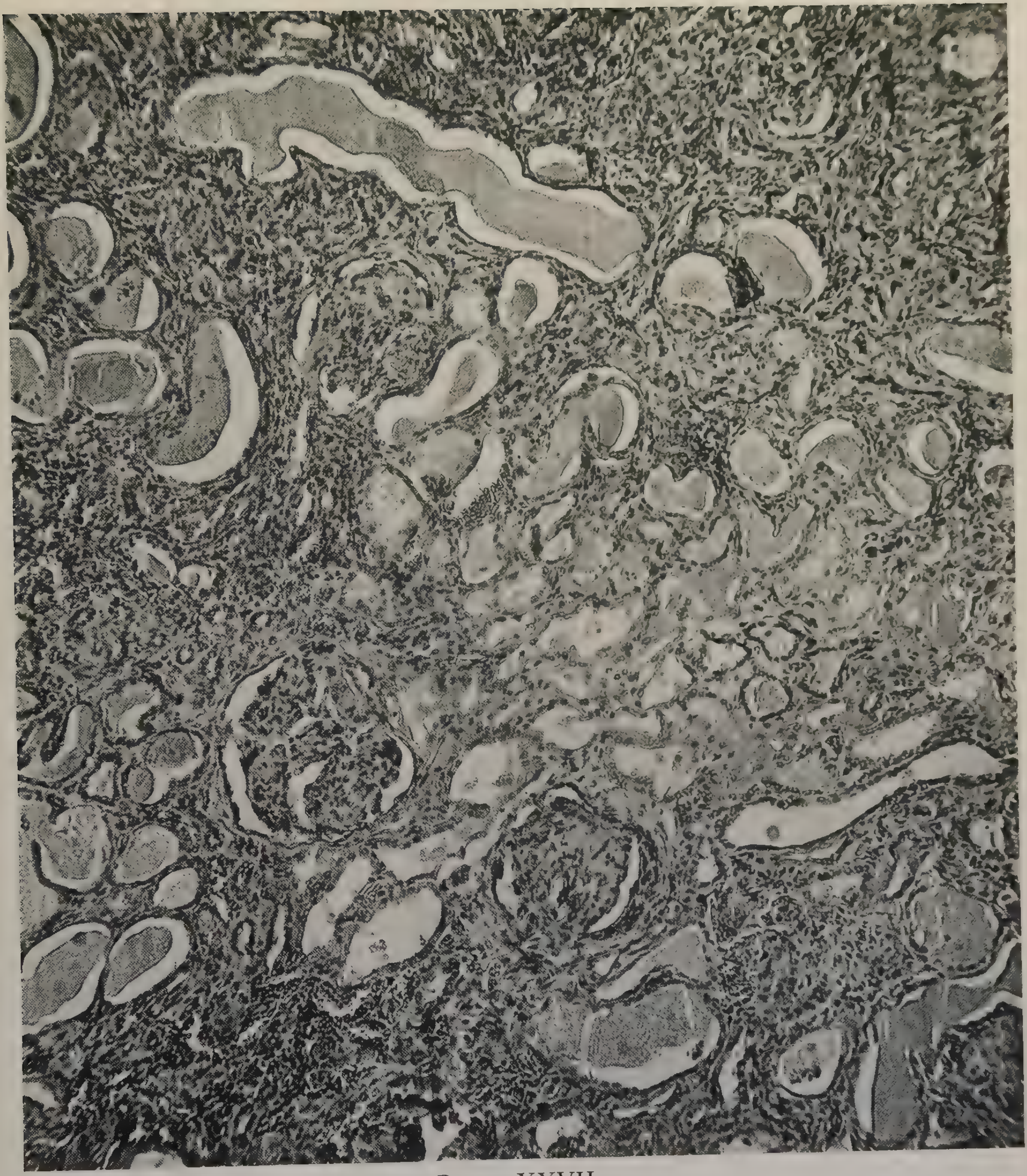

Plate XXVII b

The fibrous proliferation of the interstitial tissue has either collapsed tubules or caused a dilatation of them. There are many adhesions between the fibrous tufts and the capsule.

red blood cells and blood casts. There are many large renal failure casts in the collecting tubules.

Interstitial Tissue. Throughout the cortex there is a very marked proliferation of connective tissue with the usual destruction of the normal architecture. The tissue is quite fibrous in some areas and forms retracted scars where it reaches the surface. There is a diffuse infiltration with round cells and also with a moderate number of polymorphonuclear leucocytes. In some places this infiltration is extremely dense.

Arteries. There is a moderate fibrous thickening of the intima of the larger arteries. The small branches to the cortex are greatly thickened by new-formed connective tissue.

SUMMARY

The kidneys show old but still active inflammatory processes involving the glomeruli and interstitial tissue. The relations of the tubules are destroyed by these processes, and active degenerative processes are still observable in them. The arteries show a marked sclerosis.

CASE XXVIII

Nathaniel C. Aged fifty.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Twenty-two years. Observed during the last two years.

Etiology. No information.

Course. In 1902, twenty-two years before his death, he was told by a doctor that the examination of his urine showed that his kidneys were acutely inflamed. Although he believed that he had completely recovered insurance was refused in 1912 because there was a little albumin in the urine. He remained in good health until 1922 when retinal hemorrhages interfered with vision. At that time the urinary sediment indicated the latent stage of a glomerular nephritis. But only 31 per cent of functioning renal tissue remained, and before his death of uremia in 1924 the amount had fallen to 8 per cent of the normal.

RELEVANT CLINICAL DETAILS

The patient was unable to recollect many details of what was probably the initial stage in 1902. He remembered that he went to a doctor because he had a pain in his back and that it was after a specimen of urine had been examined that he was told that he had an acute inflammation of the kidneys. He knew nothing of any preceding infection, and apart from the transient pain in his back he remembered no other symptoms, except that his weight decreased from 230 lbs. to 156 lbs. after a month in bed with no other nutrition but milk.

From 1902 to 1922 he remained perfectly well and believed that he had completely recovered from the acute attack of Bright's disease in 1902. But in 1912 he was refused life insurance because his urine contained a small amount of albumin.

On November 15, 1922, he found that the vision in his right eye had become blurred. Ophthalmoscopic examination showed in both eyes a pronounced retinal arteriosclerosis with recent hemorrhages.

He was seen for the first time on November 23, 1922. The vision of both eyes had deteriorated and there were many linear hemorrhages along the retinal vessels. There was no very marked thickening of the radial and brachial arteries and the heart was not obviously enlarged. The blood pressure, however, was 230 systolic and 130 diastolic.

At intervals up to July 1924 measurements of the amount of functioning renal tissue gave the series in Table XXX.

Even in 1922 the blood urea concentration was well above normal and it was not possible to obtain a really concentrated urine. The highest specific gravity was 1.019 in 1922 and in July 1924 it had fallen to 1.011. But on four separate occasions one or two blood casts were found and the number of red blood cells which could still be counted was always far above normal, though the maximum was only 12,700,000 per twelve hours. Renal failure casts were present in small numbers. The rate of protein excretion varied considerably but in general tended to decrease

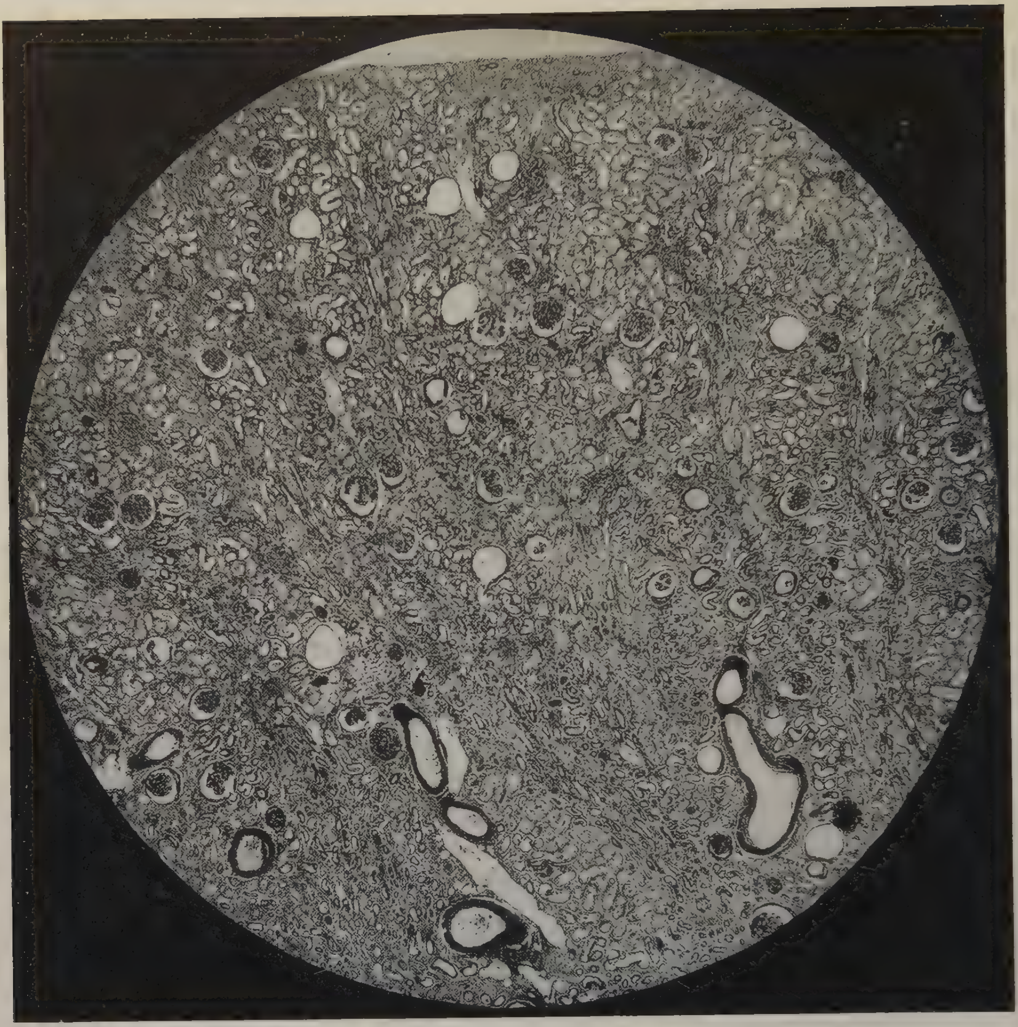

Plate XXVIII a

The inflammatory proliferation of the connective tissue is well seen. The tubules still preserve their normal relations fairly well. The glomeruli are either enlarged or shrunken. Several arteries showing definite sclerosis are present.

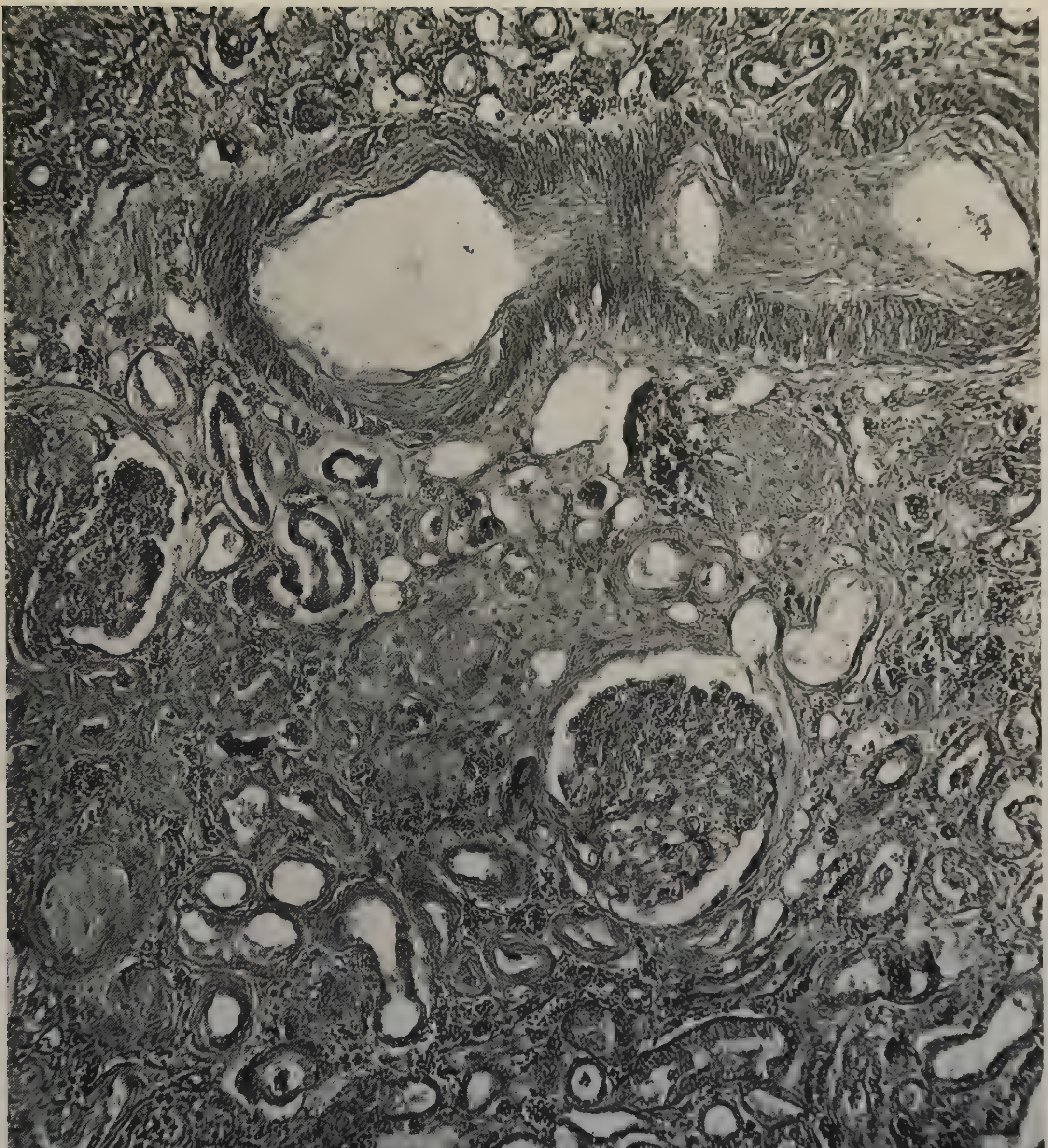

PLATE XXVIII B

The glomerular tufts are enlarged by the inflammatory reactions. There is a marked proliferaton of the interstitial tissue with deformity of the tubules. An artery is shown whose wall is greatly thickened.

Table xxx

Date	*Amount of Functioning Renal Tissue Per Cent of Normal*
1922 Nov. 23	32
1923 Mar. 23	32
July 17	20
Oct. 17	15
1924 Jan. 23	20
May 4	9
July 25	8

from a maximum of 2510 mg. in November 1922, to a minimum of 230 mg. per twelve hours in May 1924. It was thought that these urinary findings justified the hypothesis of a latent hemorrhagic lesion in kidneys which were already greatly diminished in size and were growing progressively smaller as the terminal stage approached.

During these last two years of his life the patient remained cheerful and comfortable. His vision it is true deteriorated but so slowly that he was never quite sure that it might not be improving, and in all other respects he was free from any noteworthy disability. But in July 1924 he developed an acute middle ear infection which left him obviously weaker than before, though still cheerful and hopeful. The hypertension showed a tendency to diminish as is shown in the following series which includes all the measurements made:

Table xxxi

Date	*Systolic*	*Diastolic*
1922 Nov. 23	220	130
1923 March 23	190	110
May 9	180	110
July 17	180	95
July 20	180	95
Aug. 28	180	105
Sept. 1	170	90
Sept. 19	150	80
1924 Jan. 23	160	90
May 6	185	100
July 10	160	100
July 24	145	80
Sept. 1	140	80

He was not seen at the end but his physician wrote that on October 28, 1924, he complained of severe pain in his right foot which became red, swollen and tender. With this came a rapidly deepening coma in which he died on November 4, 1924.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained after death. They were somewhat decreased in size, averaging in measurement 11 × 5 × 4 cm. The capsule stripped fairly easily, leaving a greyish pink surface which was finely granular. No gross petechial hemorrhages were seen. The cut surface showed indistinct markings. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Most of the glomeruli are still fairly well preserved. The capillaries of their tufts contain circulating blood, but the tuft as a whole shows a definite increase in nuclei. These are of fibroblasts and of mononuclear and polymorphonuclear leucocytes. Some of the tufts show areas of fibrosis and in a few the capillaries are plugged with fibrin thrombi and polymorphonuclears. Bowman's space in many instances contains granular material but no definite crescents are found. Other glomeruli, about one-fourth of the total number, are almost completely fibrous, forming small nodules of hyaline collagen.

Tubules. In the irregular scars scattered through the cortex the convoluted tubules are compressed and distorted and their epithelium is reduced to an irregular layer of atrophied cells. The tubules in the portions of the cortex more free of connective tissue proliferation are normal in shape and their epithelium is typical, but shows a widespread cloudy swelling of the milder type. The lumens of the tubules are filled with granular material. The straight tubules of the cortex contain hyaline and granular casts, but no large renal failure casts are found.

Interstitial Tissue. Throughout the cortex there are many irregular areas of marked interstitial proliferation. The tissue is fibrous, but still cellular and contains many leucocytes of both the mononuclear and polymorphonuclear type. In other places, the interstitial tissue is more nearly normal in amount, though in no place can areas be found which are entirely free of fibrosis or leucocytic infiltration. Scattered through the entire section are a moderate number, about 6 to 2 sq. cm. of section, of small ill-defined collections of polymorphonuclear leucocytes. These are present equally in the cortex and in the medulla.

Arteries. There is a marked fibrous thickening of the intima of the large arcuate arteries and of the entire wall of the smaller intrelobular vessels.

SUMMARY

The kidney shows slightly active rather old inflammatory processes in the glomeruli and interstitial tissue. The epithelium shows recent degenerative changes and the arteries are moderately arteriosclerotic. The presence of scattered (embolic?) recent abscesses leads to the suspicion that there was present some extrarenal infection which may have been the cause of coma and death rather than renal failure.

CASE XXIX

John C. Aged twenty-four.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Nineteen years. Observed during the last week.

Etiology. Probably scarlatinal streptococcus.

Course. It seems likely that the initial stage occurred in 1909 when he became edematous during convalescence from a disease which was thought to have been measles. The doctor found albumin in his urine at that time. He passed into a latent stage until December 1927 when his vision became blurred. He was seen in March 1928, nine days before his death of uremia.

RELEVANT CLINICAL DETAILS

In 1909 when he was five years old he had an illness which was supposed to be measles. But during convalescence he became edematous, especially in the face, and protein was found in the urine. The proteinuria continued for six months and then apparently disappeared. However, it was found again on several occasions during the intervening years. He had never been considered really quite strong or well, though he had no definite complaints. But he was not fit for much exertion and was repeatedly told that he was anemic.

In December 1927, eighteen years after the illness during which the proteinuria appeared, he found that his vision was blurred. During January 1928 his sight became much worse so that he was unable even to recognize faces. Vomiting, irregular in time and not associated with nausea, set in and occasional muscular twitchings were noticed. Since then his condition had steadily deteriorated and he had become extremely weak.

He was admitted to the hospital on March 19, 1928. He was pale and dehydrated. The red blood cells were 2,010,000 per cubic millimeter. There was no edema. The heart was somewhat enlarged. The systolic pressure was 174 systolic and 100 diastolic. The eyeground showed many hemorrhages and plaques of exudate.

The twelve hours' night urine had a volume of 550 c.c. with a specific gravity of 1.018. It contained 2363 mg. of protein. No casts were found. The number of red blood cells was 2,650,000 per twelve hours. There was a macroscopic pyuria, with 506,000,000 cells, mainly pus cells. The blood urea concentration was 636 mg. per 100 c.c.

In spite of intravenous injections of glucose and blood transfusion the patient rapidly became weaker, the blood pressure fell, the volume of urine decreased and he died on March 28, 1928.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained at autopsy. They were about normal in size, averaging 12 × 5 × 3 cm. The capsule was somewhat adherent and stripped with some difficulty, leaving a granular reddish purple surface. No gross petechial hemorrhages could be seen. The cut surface showed a definite narrowing of the cortex. The arteries appeared normal.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli show an old but still active inflammatory process. Many of them are half again their normal size, their tufts are infiltrated with cells, including polymorphonuclears, and also show fibrosis which distorts and obliterates the capillaries. Extensive adhesions have destroyed Bowman's space, which when it still persists contains exudate that is more or less organized. Other glomeruli are completely fibrous and reduced in size to small hyaline nodules.

Tubules. The tubules throughout large areas of the cortex are markedly distorted by the developing connective tissue. Very few can be found which approximate in form their normal appearance. In the areas of scarring they are reduced to irregular clumps of atypical epithelial cells or tortuous channels with a rudimentary lumen lined with atrophic epithelium. In the areas where the fibrosis is of lesser degree the tubules are greatly dilated. Some of them contain hyaline material and their epithelium is flattened; in others the epithelium is hypertrophied, shows some cloudy swelling with necrosis and desquamation, and the lumen contains granular material. Very few casts are present in the convoluted tubules, but there are many large renal failure casts in the collecting tubules.

Interstitial Tissue. Throughout the entire cortex there is a marked destruction of the renal architecture by the development of fibrous connective tissue in the interstitial tissue. The new tissue is fibrous, in many areas consisting of almost hyaline collagen in which are a few fibroblasts. All through this fibrous tissue there is a heavy infiltration with leucocytes. The majority of these are lymphocytes, but many polymorphonuclears are also present.

Arteries. Most of the sections through the larger arcuate vessels are essentially normal. Some, especially those embedded in scar tissue, show a fibrous thickening of their intima. The smaller interlobular branches show this same relation of fibrous thickening of their wall to areas where the inflammatory process is most pronounced.

SUMMARY

The kidney shows old and far advanced but still active inflammatory processes in the interstitial tissue and glomeruli. The architecture of the cortex is destroyed, and there are active degenerative processes in the epithelium. The arteries are sclerotic.

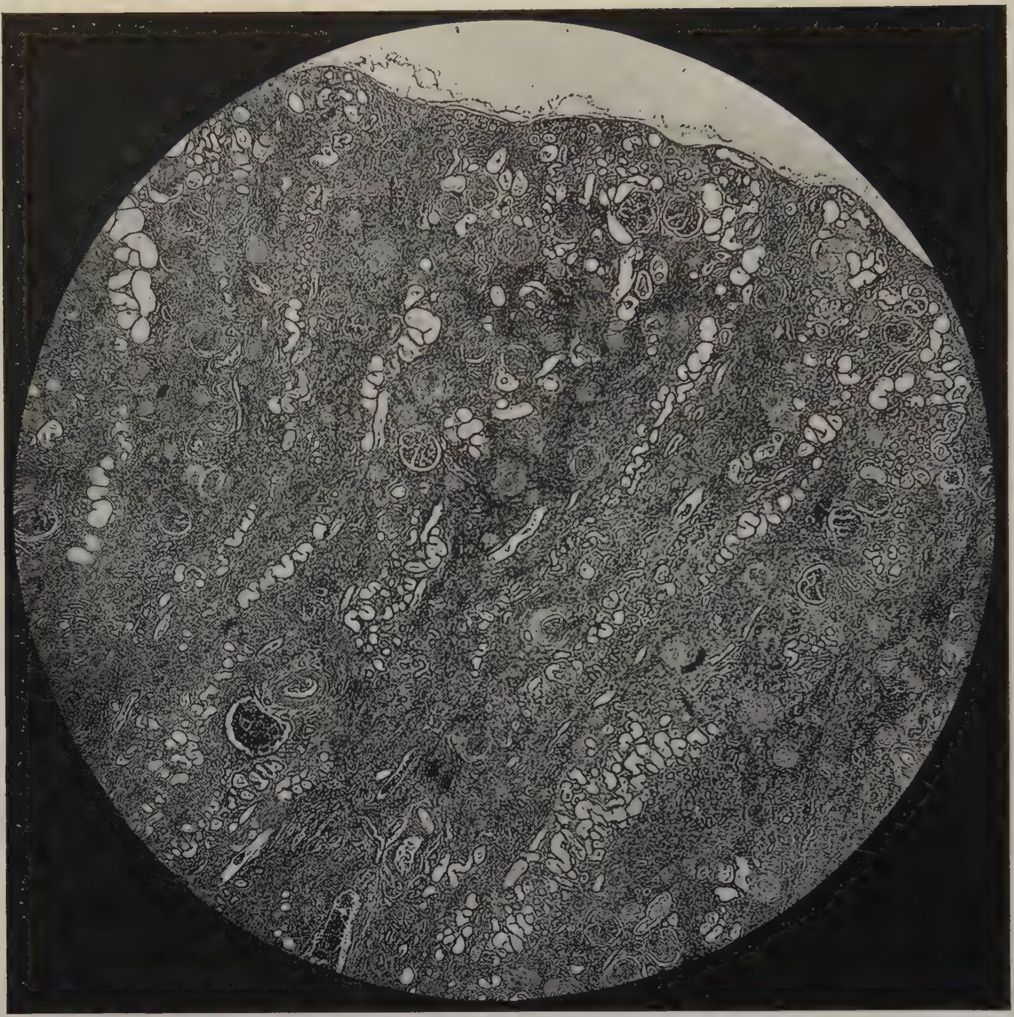

Plate XXIX a

There is a marked irregular proliferation of the framework of the kidney with scattered areas of leucocytic infiltration. The tubules have almost completely disappeared in some areas and are greatly dilated in others. The glomeruli are greatly enlarged or are fibrous and can be made out only with difficulty. The arteries are sclerotic.

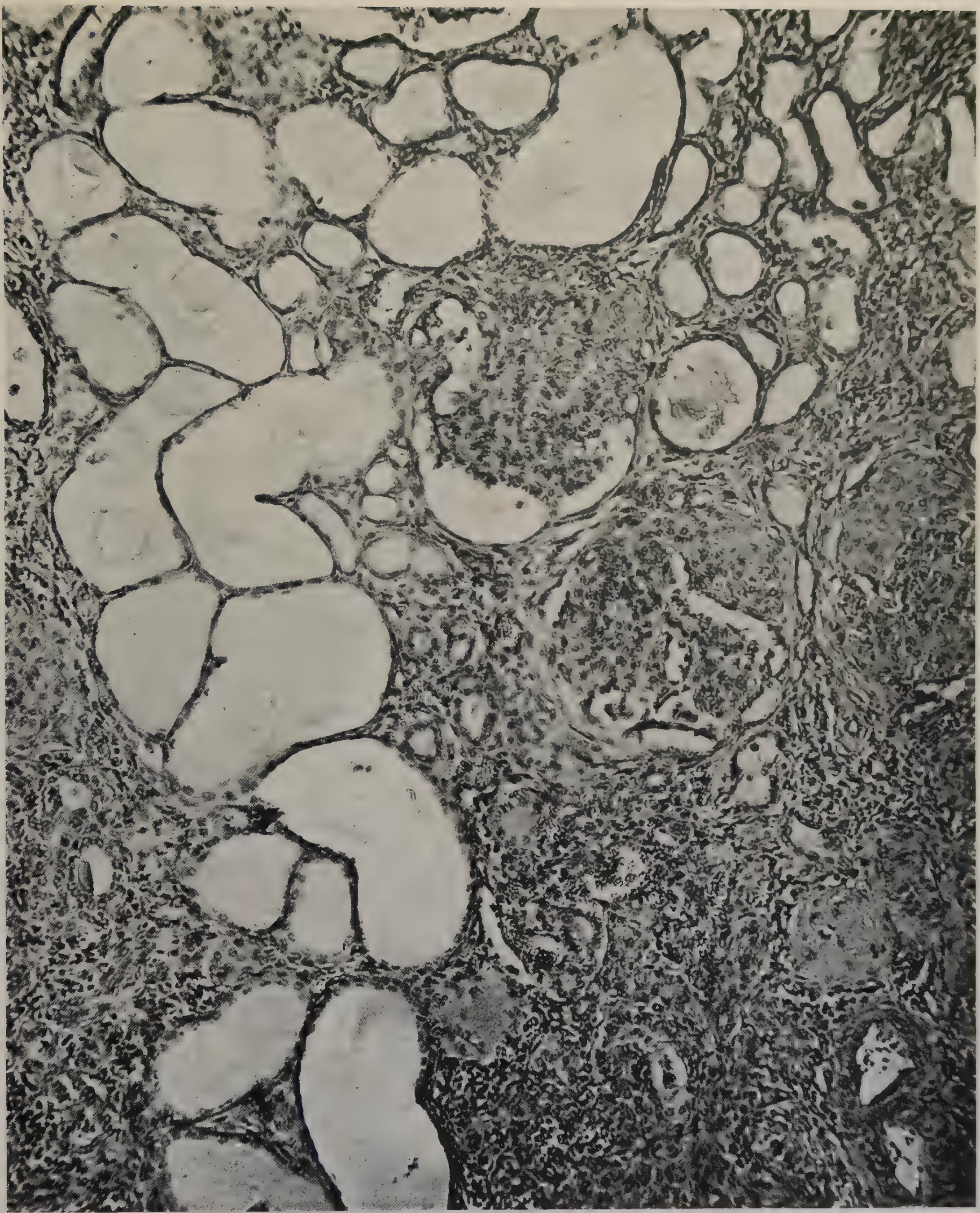

Plate XXIX b

Three enlarged fibrous glomerular tufts are seen. The extreme proliferation and leucocytic infiltration of the interstitial tissue has completely destroyed the tubules in some regions whereas in others they are greatly dilated and filled with colloid material. (Cf. Plate xcv.)

CASE XXX

Lucy C. Aged thirty-one.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Six and three-quarter years.

Etiology. Developed during convalescence from a fever diagnosed as influenza.

Course. In October 1920 after "influenza" she became edematous and was found to have slight hypertension. The urine contained blood and albumin and nephritis was diagnosed. It seems likely that this was the initial stage. There were no symptoms from 1920 to 1924, but in 1923 her blood pressure was found to be above normal. In 1924 there was a transient hemiplegia and pronounced hypertension was noted. In August 1925 evidence of an active inflammatory lesion was found. The amount of renal tissue was reduced to 41 per cent. In August 1926 symptoms of uremia developed but the patient did not die until November.

RELEVANT CLINICAL DETAILS

In February 1920 she consulted a genitourinary surgeon on account of hematuria. The following facts were taken from the notes he made at that time. A short time before the blood appeared in the urine there had been a fever which was supposed to be influenzal. During her convalescence she noted the red or brown color of the urine and found that her legs were swollen. On examination her blood pressure was found to be 144 systolic and 98 diastolic. There was evidence of an inactive tuberculosis of the left lung. A catheterized specimen of urine was bloody. Several routine urine examinations all showed a heavy cloud of albumin. The ureters were catheterized and blood and albumin were found to be coming from both kidneys. No evidence of renal tuberculosis was discovered, but Bacilli coli were found in the urine. In 1918, however, she had had a pyelitis with hematuria and renal colic during pregnancy. The blood urea concentration was 108 mg. per 100 c.c. Phenolsulphonephthalein excretion was 27.5 per cent in two hours. A diagnosis of nephritis was made. The hematuria and edema disappeared quickly. These facts are in favor of the supposition that during February 1920 she passed through the initial stages of a glomerular nephritis.

From 1920 to 1924 there were no symptoms and it seems likely that this was the period when the renal lesion was in the latent stage. In 1923, however, a chance examination showed that the blood pressure was "a little higher than normal."

During 1924 she began to suffer from headaches and was under treatment for hypertension.

She was first seen in August 1925. She was complaining of severe headaches. Her blood pressure was 230 systolic and 160 diastolic. There was no edema. The arteries were not obviously thickened. The urine contained 2690 mg. of protein in twelve hours, 222,000 casts of which 2 per cent were fatty, 2 per cent waxy and the rest hyaline. The number of red blood cells was 54,000,000, and there were 13,000,000 white blood cells and epithelial cells. This was interpreted as indicating an active inflammatory and degenerative renal lesion. It had led to an extensive destruction of the kidney for the ratio test showed that only 41 per cent of the expected amount of renal tissue was still functioning.

During the next year she was seen several times and was symptomatically much improved but there was no evidence of any radical change in the nature or activity of the renal lesion. On the other hand there seemed to be no rapid progression, for, in April 1926, her blood urea concentration was only 54 mg. per 100 c.c. The blood pressure never fell below 220 systolic and 140 diastolic.

In August 1926 she quite suddenly felt weak and for several days stayed in bed. There was occasional vomiting without much nausea. When she got up she was dyspneic on exertion and had some cough with expectoration. Throughout September and October these symptoms continued unchanged except that she became perceptibly weaker. On November 5 her muscles began to twitch and on the eleventh generalized clonic convulsive movements lasted for two minutes.

On November 13 she reentered the hospital. She was conscious but very restless. The muscles were incessantly jerking and her eyes were staring. There was frequent vomiting. The pulse was strong and regular, the blood pressure 170 systolic and 120 diastolic. She was edematous to the waist and there was fluid in the right pleural cavity. The volume of urine for twelve hours was 127 c.c. with a specific gravity of 1.015. The specimen contained 28,500 casts which were all renal failure casts. The number of red blood cells was 85,000,000 and there were 162,000,000 white blood cells and epithelial cells. On November 15, 1926, the blood urea concentration was 216 mg. per 100 c.c. She died in coma on November 17.

PATHOLOGICAL OBSERVATIONS

There was a moderate edema of the feet and ankles present at autopsy and a small amount of clear fluid in the serous cavities. The heart was twice its normal size, and the valves were normal. Scars were found at both apices and in the right upper lobe was a recent caseous focus 1.5 cm. in diameter. The left kidney was small, measuring 8.5 × 4 × 2.5 cm. The capsule was adherent and the surface of the kidney distinctly granular and of mottled yellow and purple color. The cut surface showed a narrow cortex. The pyramids were congested and the renal artery considerably thickened. The right kidney was the same as the left.

The abdominal arteries and aorta contain many yellow spots in their intima and the former showed a definite thickening of their walls. The remaining organs presented no significant lesions.

MICROSCOPICAL EXAMINATION

Sections of the spleen and liver showed a marked passive congestion. Sections of the aorta showed a marked fibrous thickening of the intima with fatty degeneration.

Kidneys: *Glomeruli.* Not a single glomerulus could be found that was even approximately normal in appearance. Most are completely infiltrated with connective tissue and transformed into hyaline masses though in some the connective

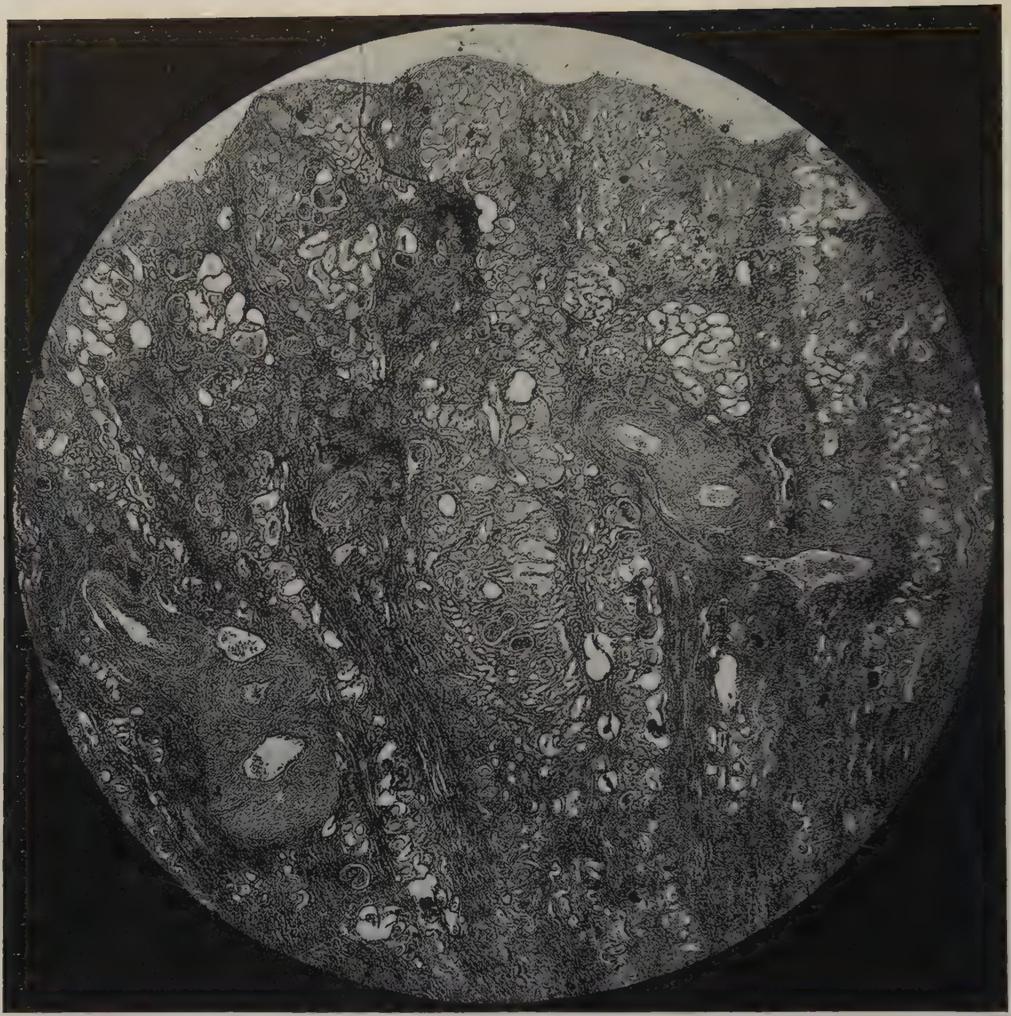

Plate XXX a

There is an extreme and irregular proliferation of the connective tissue with diffuse round cell infiltration. Clustered groups of tubules are dilated and filled with colloid. It is very difficult to find any of the fibrosed glomeruli at this magnification. The arteries show a marked sclerosis and the granulation of the surface of the kidney is very apparent.

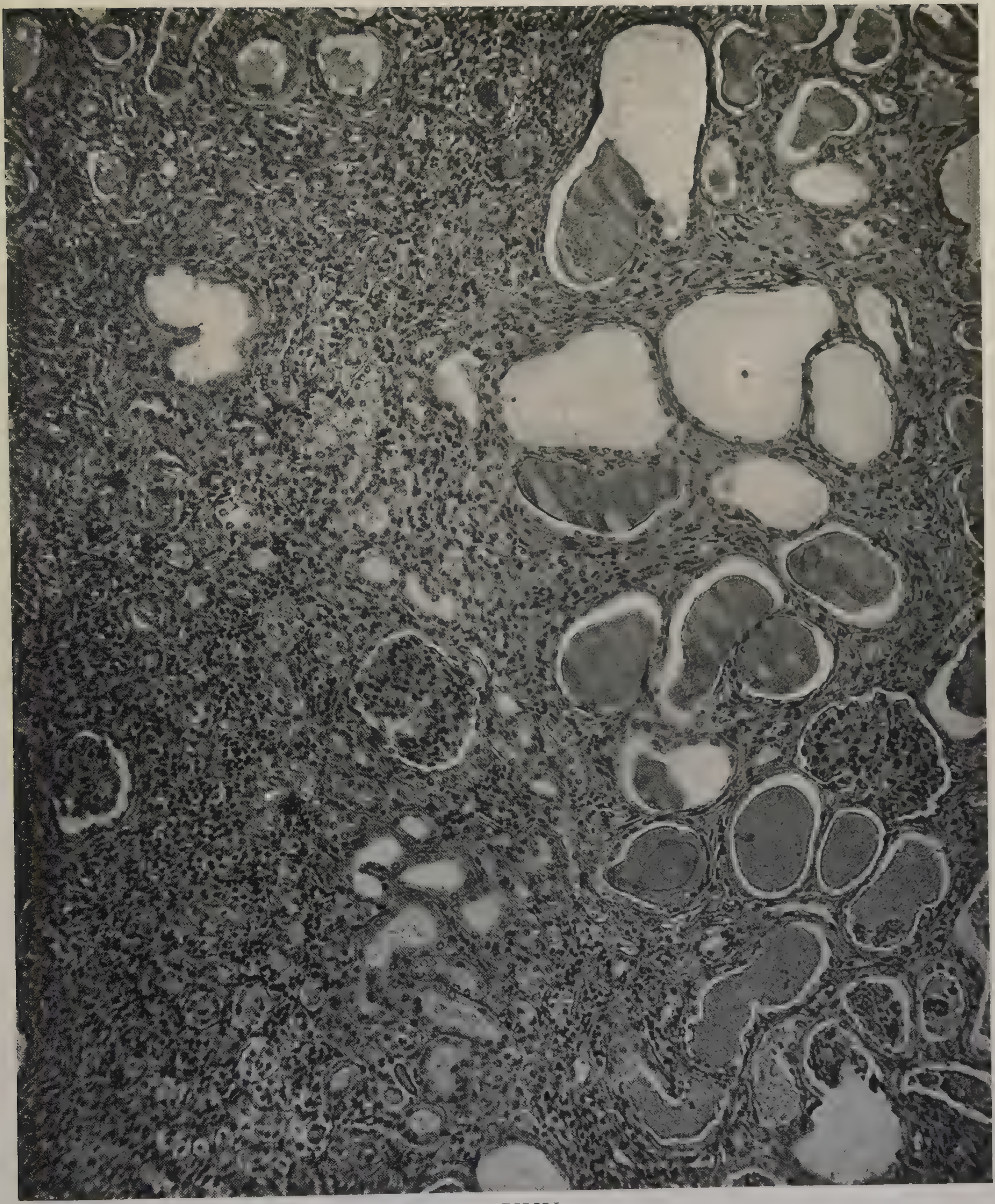

Plate XXX b

The glomeruli are fibrous and shrunken. The fibrosis of the interstitial tissue has caused a collapse of many tubules whereas others show a compensatory hypertrophy.

tissue is still fairly cellular. In neither case, however, is there any trace of Bowman's space remaining.

Tubules. The convoluted tubules of the cortex are markedly involved by the diffuse development of connective tissue throughout the cortex. The majority are greatly compressed and the lumens are obliterated so that they exist only as solid cords of atrophic cells. Other tubules are dilated and their distended lumens, lined by a flattened epithelium, are filled with coagulated material and hyaline or granular casts. Occasionally, red blood cells are seen. The epithelium of both types of tubule shows various types of degeneration. Fatty degeneration is particularly marked in the collapsed solid tubules.

The ascending limbs of Henle's loop show the same changes. The epithelium of the collecting tubules is more nearly normal, but many hyaline, granular and broad renal failure casts are present in their lumens.

Interstitial Tissue. Throughout the cortex and also in the medulla there is a very marked fibrous proliferation of the interstitial tissue. Almost solid areas where the convoluted tubules are collapsed alternate with areas where proliferation is less marked and the tubules are dilated as already described. Throughout the new-formed connective tissue is a heavy round cell infiltration, the cells of which consist almost entirely of lymphocytes.

Arteries. There is a marked fibrous thickening of the intima of all the arteries. The finer arterioles in the cortex are almost completely obliterated by the process. Around the large branches between the cortex and medulla there is a considerable perivascular connective tissue proliferation and round cell infiltration.

SUMMARY

The kidneys show an almost complete destruction of the glomeruli by the advanced inflammatory process which is associated with an extreme interstitial proliferation. The collapsed or cystic tubules show severe degeneration of their epithelium and there is an extreme sclerosis of the arteries.

CASE XXXI

Richard C. Aged forty-five.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown.

Etiology. No information.

Course. No history which threw any light on the previous course of the condition was obtained. The patient believed that he had been in excellent health three weeks before his death in uremia. It was noted then that he was pale and weak and shortly afterwards vomiting began. There was slight edema of the legs. The heart was not obviously enlarged nor were the radial and brachial arteries greatly thickened. The blood pressure was 136 systolic and 84 diastolic. The hemoglobin was 30 per cent and the corpuscles occupied only 11.4 per cent of the blood volume after centrifugalizing. The amount of renal tissue was estimated as about 5 per cent of the normal. The blood urea concentration rose from 331 mg. on January 31, 1923, to 413 mg. on February 7, and on February 14 just before his death the concentration had risen to 503 mg. per 100 c.c. of blood.

Even after abstention from fluids the urine had a specific gravity of only 1.010. The number of casts in twelve hours' urine was 114,000, and all the casts were of the renal failure type. Red blood cells were present in abnormal numbers and were found incorporated in some of the casts. The rate of protein excretion was 1020 mg. per twelve hours.

The diagnosis of the terminal stage of a previously unrecognized hemorrhagic Bright's disease was made.

PATHOLOGICAL OBSERVATIONS

Autopsy showed an old quiescent chronic pulmonary tuberculosis and a secondary anemia. As terminal infections there were present an acute pleurisy, a furuncle of the skin of the neck and bronchopneumonia.

The kidneys were definitely small, averaging 10 × 4 × 2.5 cm. The capsule stripped with some difficulty, leaving a deep purplish granular cortex. The cut surface showed a reduction of the cortex and indistinct markings. The renal arteries were somewhat thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli show varying stages of a glomerulitis. Many are reduced by the proliferation of connective tissue in the tuft to hyaline nodules, while in others the process is of a milder degree. The tuft is infiltrated with leucocytes, both mononuclears and polymorphonuclears, and there is a proliferation of fibroblasts and varying degrees of collagen formation. Bowman's space is as a rule obliterated by fibrous adhesions, but an occasional glomerulus can be found in which the space is filled with exudate or red blood cells.

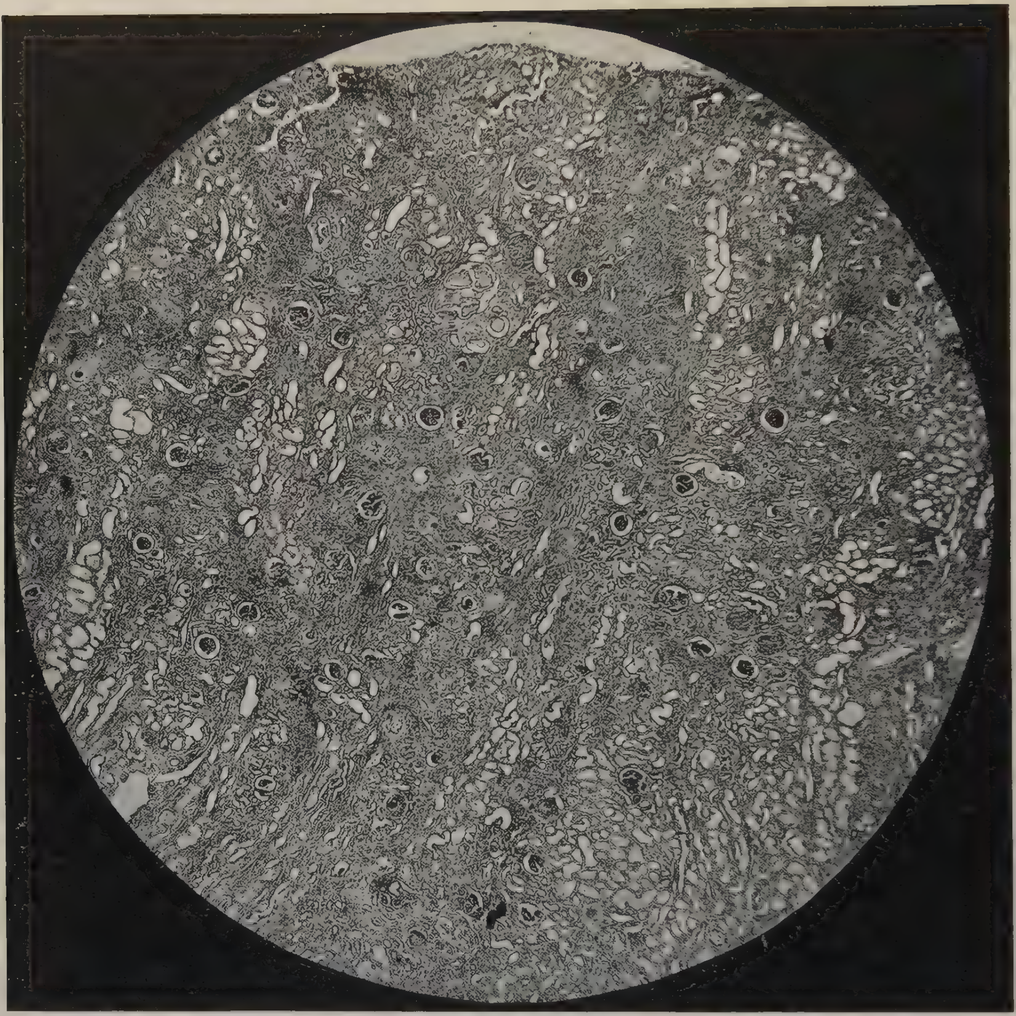

Plate XXXI a

Scattered glomeruli are still seen in various stages of inflammatory destruction. The connective tissue of the framework of the kidney shows the usual inflammatory proliferation which destroys the tubules in some areas and causes their dilatation in others.

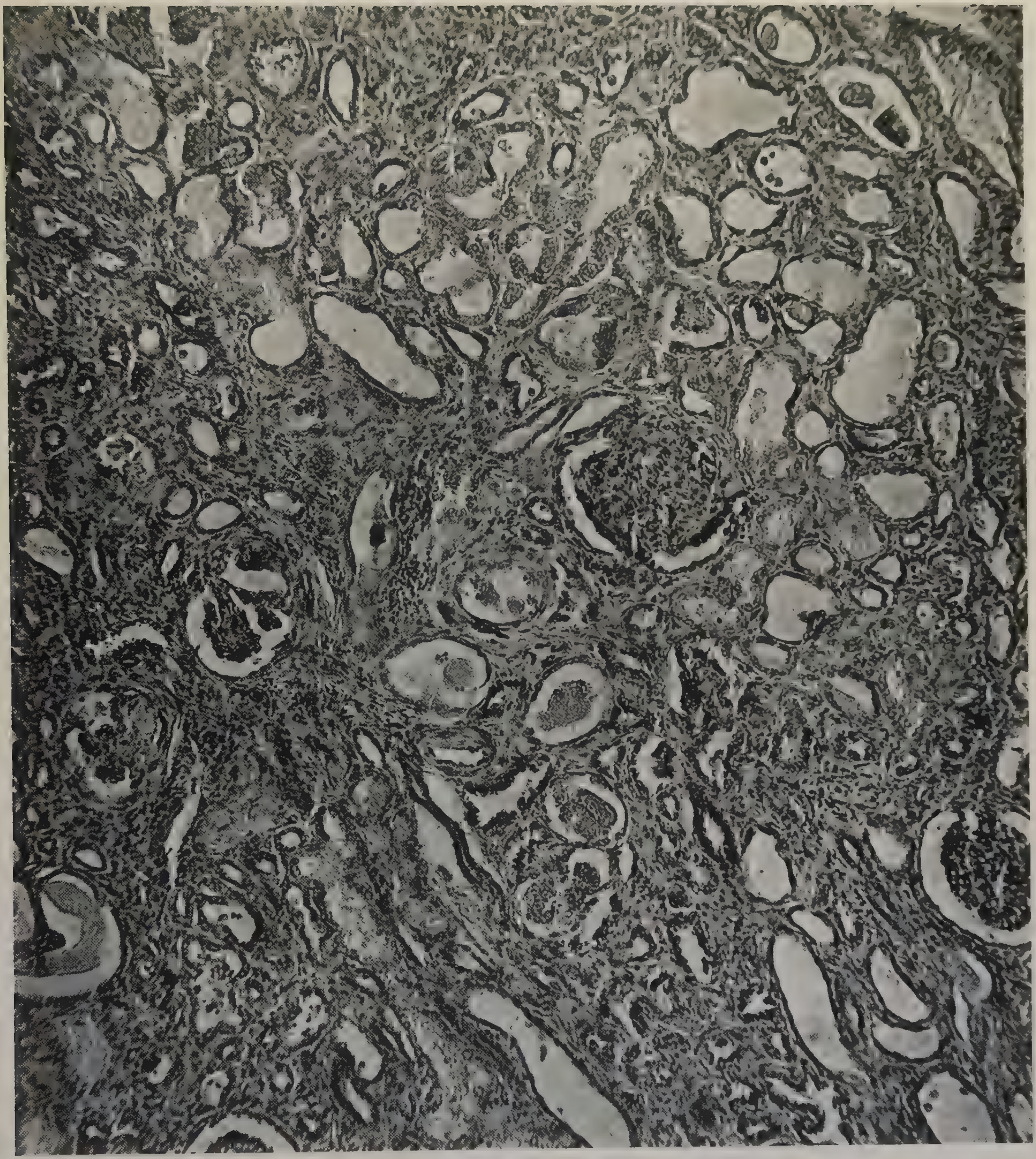

PLATE XXXI B

Distorted fibrous glomeruli whose capsular spaces are obliterated by adhesions, are seen. The fibrosis and leucocytic infiltration of the interstitial tissue has caused the usual distortion of the tubular architecture. Epithelial degeneration is extensive.

Tubules. Groups of convoluted tubules still persist in the fibrosed cortex which have a fairly normal morphology. Some of these are larger than normal and lined with a hypertrophied epithelium which in many places shows cloudy swelling. Their lumens are filled with granular material. Throughout the cortex however are even larger areas where the connective tissue development has produced irregular distortion and collapse of the tubules, or on the other hand a cystic dilatation with the inclusion of colloid in their lumens. In some of the more normal tubules are found hyaline and granular casts as well as red blood cells and blood casts. In the collecting tubules are many renal failure casts.

Interstitial Tissue. The cortex is diffusely infiltrated with fibrous connective tissue which is still fairly cellular. There are heavy infiltrations with both mononuclear leucocytes and a lesser number of polymorphonuclears. The entire normal relation of the tubules and glomeruli is altered by the process. Where the connective tissue reaches the free surface retracted scars are formed.

Arteries. The arcuate arteries show a varying amount of fibrous thickening of their intima. In some, those lying in the midst of cellular scars, the sclerosis is marked, while in others the intima is more nearly normal. The smaller vessels are also normal, except where their thickened walls lie in heavy scars.

SUMMARY

The kidney shows a severe chronic inflammatory process affecting the glomeruli and interstitial tissue. The activity of the process is indicated by glomeruli hemorrhages and the presence of polymorphonuclear leucocytes. The tubules are atrophied in large areas of the cortex; those more normal in structure show parenchymatous degenerations. The arteries show an irregular sclerosis.

CASE XXXII

William C. Aged thirty-five.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Twenty-seven years. Observed for six months before death.

Etiology. Scarletinal streptococcus.

Course. The renal lesion probably began during convalescence from scarlet fever twenty-seven years before his death, but the diagnosis of Bright's disease was not made until twelve years later. He was not seen until the terminal stage was well advanced. The blood urea concentration was then 293 mg. per 100 c.c. The urine contained only renal failure casts. There were 13,000,000 red blood cells per twelve hours. He died six months later after an unexpected recession in the degree of uremia.

RELEVANT CLINICAL DETAILS

In 1903 when he was eight years old he and three other boys developed scarlet fever. They were all treated by cold water baths. The patient stated that all four of them subsequently developed Bright's disease and that his three friends died many years later from uremia. However the only abnormality he noted during convalescence was a rather severe arthritis. He knows that the urine was not examined and he remembers nothing of any edema. His general impression, however, was that he had not been in completely good health since that illness, though he never consulted a doctor. He knew nothing of any renal disease until 1917 when he tried to join an Officer's Training Camp and was rejected on a diagnosis of nephritis.

In 1918 he had pneumonia during the influenza epidemic. Dr. Glover who treated him then found evidences in the urine of a very active nephritis. This pneumonia was his only serious illness for he remained in fair health until early in 1929 when he began to suffer from severe headaches. It was found then that his systolic blood pressure was constantly over 200.

On November 18, 1929 he had a convulsion and lost consciousness. Later he became semiconscious but was irrational. He was given nothing but fruit juices for eleven days. He was then driven 500 miles in a hearse to San Francisco, and was seen first on November 29, 1929. He was lying flat in bed, restlessly turning from one side to the other, scratching repeatedly, and showing occasional involuntary jerky movements of the limbs, talking constantly in a disconnected way but only occasionally responding to questions. All reflexes were hyperactive. There was a pronounced pallor of the mucous membranes. No edema was present. The heart was enlarged to the left, the palpable arteries seemed to be thickened. The blood pressure was 210 systolic and 130 diastolic. There were no retinal hemorrhages or exudate. The blood urea concentration was 290 mg. per 100 c.c.

A twelve hours' urine had a volume of 968 c.c. with a specific gravity of 1.012. The rate of protein excretion was 1985 mg. per twelve hours. Only 3250 casts per

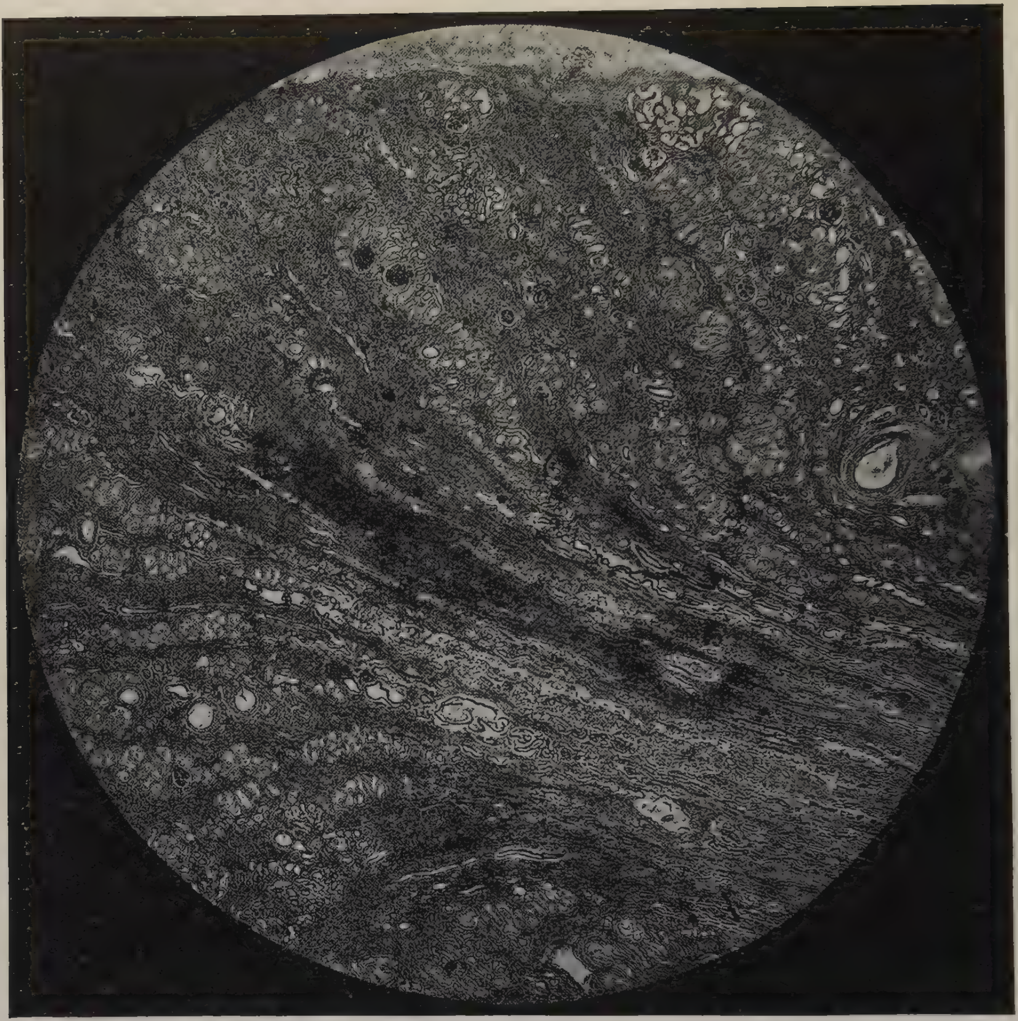

Plate XXXII a

There is a marked proliferation of the interstitial tissue in which remain islands of tubules and glomeruli. The dark regions in the center of the field are areas of intense leucocytic infiltration. Note the sclerotic artery at the right of the figure.

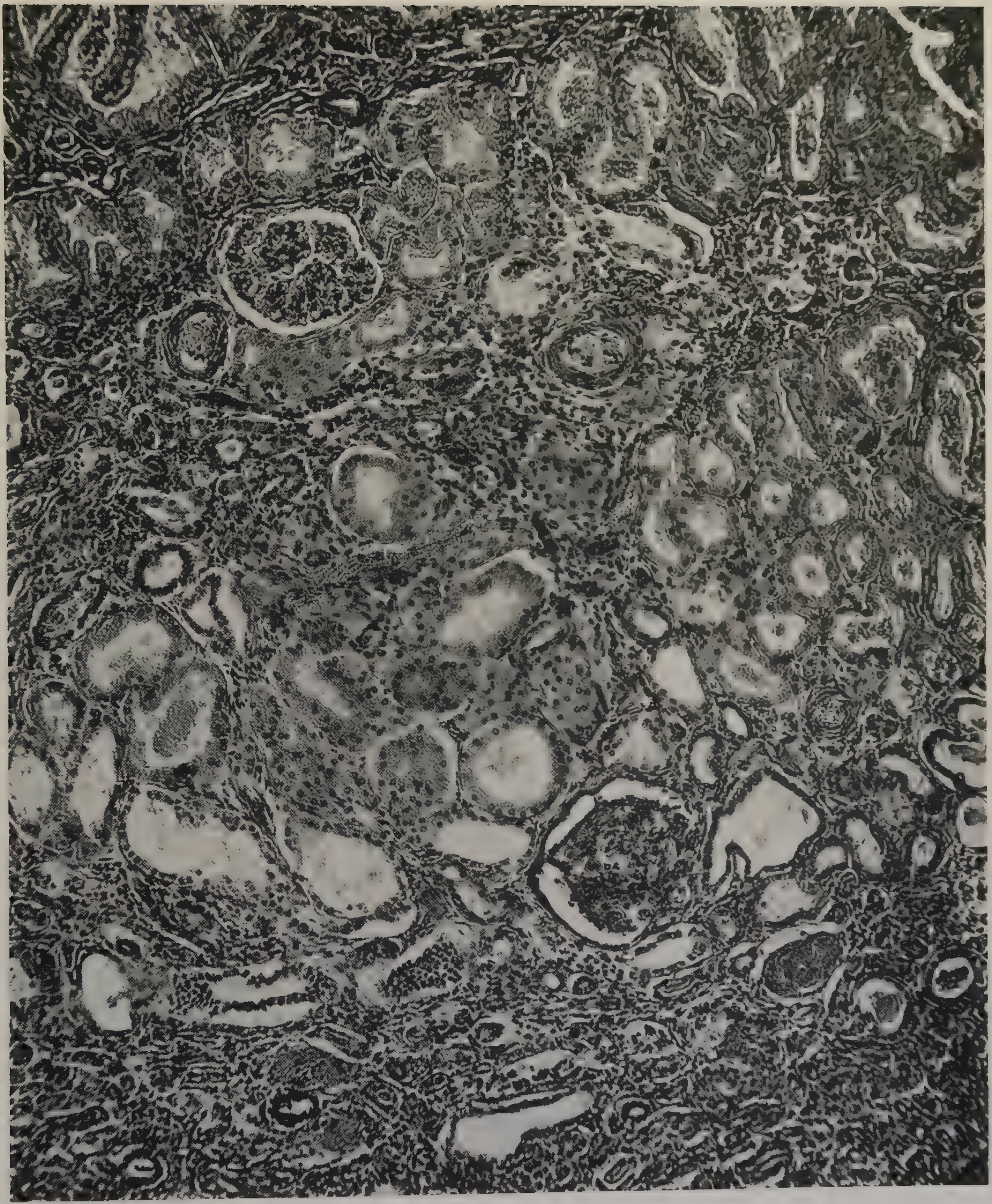

Plate XXXII b

Two glomeruli with fibrous tufts and capsular adhesions are present. A group of tubules is fairly well preserved; others are atrophied and compressed by the proliferating interstitial tissue.

twelve hours were counted. They were all renal failure casts. The red blood cells numbered 20,000,000 per twelve hours and the white blood and epithelial cells 3,200,000.

He was given sugar intravenously, and as many calories by mouth as was possible. After four days there was a very marked clinical improvement although the blood urea concentration remained above 275 for thirty days, long after the patient was up and about. Then, without any change in the urinary sediment, the blood urea concentration also fell and in the next two months went as low as 159. In spite of a still increasing sense of well-being the concentration rose and in the next two months again reached 275 mg. per 100 c.c. He then went back to work on his ranch. He was able to do a little, though he was bothered by the itching of his skin. But after another two months he experienced an extreme lethargy and weakness and returned with a blood urea concentration of 553. He became unconscious and died a few days later in coma.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained at autopsy. They were somewhat small, measuring 8 × 4 × 3 cm. Their capsules stripped with some difficulty, leaving a reddish brown finely granular surface in which no hemorrhages could be seen. The cut surface showed a marked narrowing of the cortex which was rather fibrous. The renal arteries were distinctly thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are involved in various stages of the inflammatory processes. Some are quite large, and there is a marked leucocytic infiltration of their tufts. Others are reduced in size and the tuft is more or less fibrous while many, about half the total number, are reduced to small hyaline fibrous nodules. Bowman's space is filled with organized masses of exudate or is obliterated by fibrous adhesions. Some of the tufts show a marked congestion of those capillaries which persist and in some instances there has been an escape of red blood cells into Bowman's space.

Tubules. In irregular areas throughout the cortex there is extensive distortion, collapse and atrophy of the convoluted tubules. Their epithelium consists either of atrophic cells or of a very immature irregular regenerated epithelium. Scattered throughout this background of atrophic parenchyma are irregular islands where the convoluted tubules are of normal shape and either of normal or increased size. The epithelium of these tubules shows various degenerative processes ranging from a cloudy swelling to a frank necrosis. Beside these hypertrophied tubules there are also a lesser number where the increase in size is due to a dilatation of the lumen. Casts of all sorts including an occasional blood cast are found in the convoluted tubules. In the collecting tubules there is a marked desquamation of the epithelium and many poorly consolidated broad renal failure casts are present.

Interstitial Tissue. There is a very irregular patchy proliferation of the interstitial tissue which has caused the replacement of the tubules previously described. This inflammatory tissue is quite fibrous and shows a heavy infiltration with inflammatory leucocytes, mostly of lymphocytes but also containing a few polymorphonuclears. In some areas this infiltration is extremely dense, blotting out all details of the tissue in which the leucocytes lie. Where the fibrous tissue reaches the surface retracted scars are formed.

Arteries. The larger arcuate arteries show a moderate irregular fibrous thickening of their intima and the smaller interlobular branches, which run into the cortex, also show a moderate fibrous thickening of their wall.

SUMMARY

The kidneys show old chronic inflammatory lesions in the glomeruli and interstitial tissue. The leucocytic infiltration in the interstitial tissue is extreme. The epithelium shows rather marked degenerative processes of all kinds. The arteries show a moderate sclerosis.

CASE XXXIII

Stewart D. Aged twenty-three.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Twelve years. Observed during the last three months.

Etiology. Scarlatinal streptococcus.

Course. There is a clear history of glomerular nephritis following scarlet fever in 1907, an illness from which he never completely regained his former health. He was accepted for the army during the war but only for home service as an orderly. In November 1918 he had a mild influenza and it was then found that he had a serious renal lesion. He was already uremic when first seen on March 20, 1919 but did not die until two months later.

RELEVANT CLINICAL DETAILS

In 1907, when he was twelve years old, he was kept in bed for many months after scarlet fever. He does not remember anything very clearly except that the doctor told his mother that he had kidney disease and also that for a time there was something wrong with his eyes, and that for three days he was practically blind. He is sure, however, that from that time onwards he has never been strong, and particularly that his color has never been good and that he has suffered from shortness of breath on exertion and precordial pain. When he left school he got a "sitting-down" job in a factory as a drill-grinder. In June 1918 he tried to enlist but was refused. Later, however, he was accepted for the spruce division. In fact, however, he acted as a diningroom orderly during his active service. In November 1918 he was sent to the hospital because of a mild influenza and he was then told that he had kidney disease and had not been allowed to get out of bed since then, although he himself had not been conscious of feeling any worse than usual.

When seen on March 20, 1919, he was very weak and pale. The red blood cells numbered 1,910,000 per cubic millimeter. There was no edema. An *x*-ray of the heart showed that it was greatly enlarged, much more so than the palpation and percussion disclosed. The radial and brachial arteries were much thickened. The blood pressure was 140 systolic and 100 diastolic. An oculist reported that there was no noteworthy retinal abnormality.

A concentration test gave a volume of 375 c.c. per twelve hours with a specific gravity of 1.008. A considerable amount of albumin was present but no quantitative measurement was made. The urinary sediment contained a considerable number of red blood cells and of epithelial cells, along with a moderate number of casts which were all of the renal failure type.

The blood urea concentration on March 20 was 391 mg. per 100 c.c. There was no excretion of phthalein.

In spite of the very serious condition disclosed by these observations of March 20 the patient lived on until May 23. There was increasing weakness and stupor with vomiting and epistaxis. A few days before his death signs of congestion were observed at the base of the right lung.

PATHOLOGICAL OBSERVATIONS

Only the kidneys could be examined after death. They were definitely small, averaging 8 × 4 × 3 cm. The capsule stripped with some difficulty, leaving a scarred granular surface of a greyish pink color. No petechial hemorrhages could be seen. The cut surface showed a marked reduction in the breadth of the cortex. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Those glomeruli which still persist with some resemblance to their normal appearance show a marked increase in the nuclei of the tuft. The increased cells are composed of fibroblasts, as well as mononuclear and polymorphonuclear leucocytes. There is a diffuse proliferation of connective tissue in the tuft itself which also extends and forms fibrous adhesions to the capsular wall or obliterates Bowman's space. No recent exudate or crescents are present. The remaining glomeruli are completely fibrosed and reduced to hyaline masses which are often difficult to find, lost as they are in the proliferating connective tissue of the interstitial framework.

Tubules. In large areas of the cortex the convoluted tubules are almost completely destroyed by the marked increase in connective tissue. They are seen as groups of atrophic cells with no, or only a rudimentary, lumen. In other areas the lumen is greatly dilated, contains hyaline material and is lined by a thin endothelial-like layer of cells. In still other groups of tubules whose epithelium is of the normal type there is a definite hypertrophy. This thick epithelium shows a cloudy swelling and in patches a fatty degeneration and the lumen of the tubules contains granular material. In some of the tubules are hyaline or granular casts, and in an occasional one red blood cells or polymorphonuclear leucocytes can be found. There are many large renal failure casts in the collecting tubules.

Interstitial Tissue. Throughout the cortex there is an extreme proliferation of the interstitial tissue. This tissue is quite fibrous, but still contains many fibroblasts. There is a diffuse infiltration with mononuclear leucocytes, concentrated in scattered foci to form dense masses of nuclei. Among these leucocytes are a considerable number of polymorphonuclears. Where this fibrous tissue reaches the free surface retracted scars are formed, and between these scars lie the cystic or hypertrophied tubules previously described.

Arteries. The arcuate arteries show a fibrous thickening in their intima of irregular distribution which is very marked in some vessels while in others the intima is more nearly normal. The interlobular arteries also show the same fibrous thickening of their walls.

SUMMARY

The kidneys show an old, judging from the presence of red blood cells and polymorphonuclear leucocytes, still active chronic inflammation of the glomeruli and interstitial tissue. The tubules are compressed and there are also moderate active degenerative processes present in their epithelium. The arteries show a moderate sclerosis.

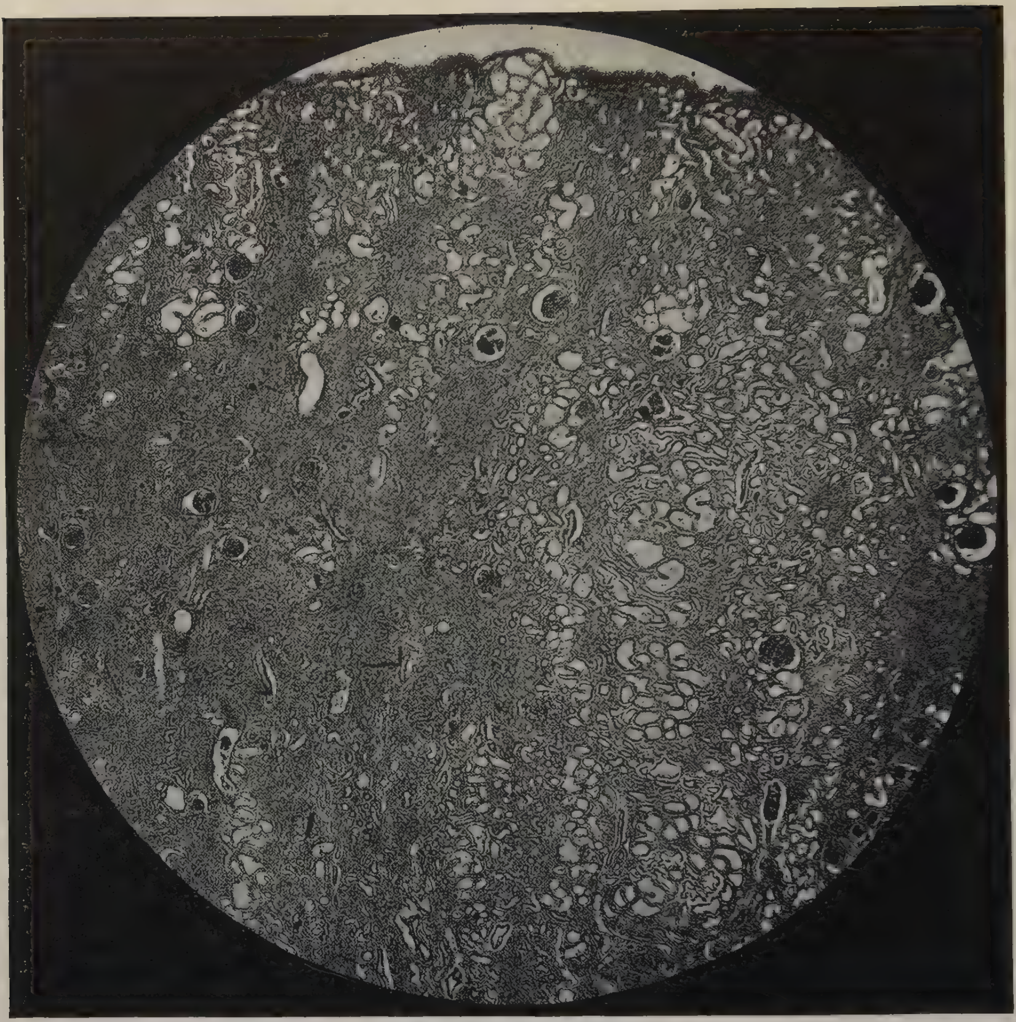

PLATE XXXIII A

There is an unevenly distributed fibrosis of the kidney framework. The tubules have almost completely disappeared in parts of the section while in others they are greatly dilated or hypertrophied. The glomeruli show all stages of the inflammation from the earlier changes with enlargement to fibrosis and contraction.

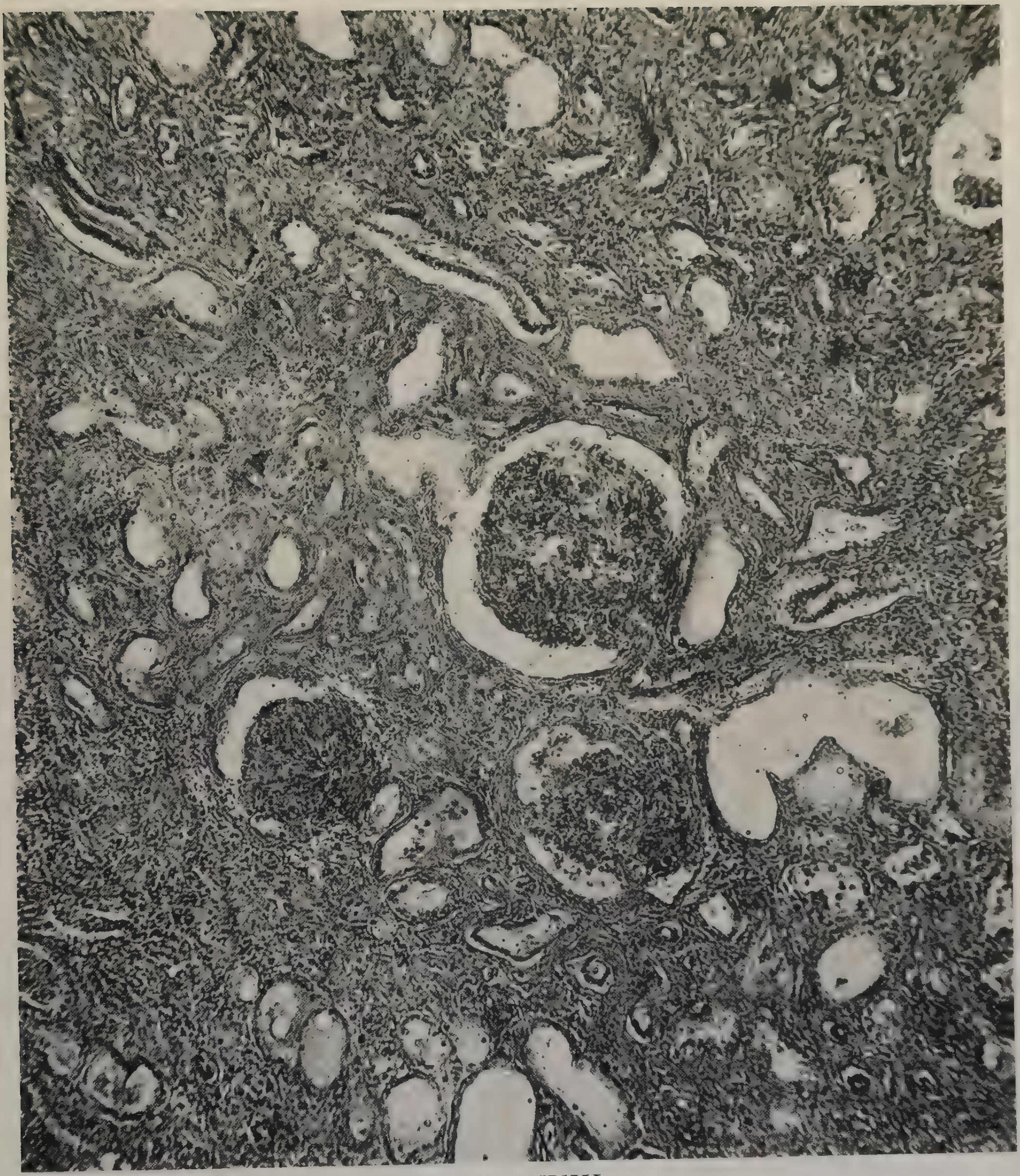

Plate XXXIII b

The glomerular tufts are heavily infiltrated with inflammatory leucocytes. The same leucocytic infiltration extends throughout the interstitial tissue with the usual deforming effect on the tubules.

CASE XXXIV

Edith D. Aged fifteen.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Six years. Observed during the last one and one-half years.

Etiology. Tonsillitis.

Course. The initial stage was marked by typical urinary changes, but there was no edema. There was apparently no active stage although on two occasions transient edema was noted. The latent stage merged gradually into a well-defined terminal stage with death in uremia.

RELEVANT CLINICAL DETAILS

In 1920 the child suffered from a severe tonsillitis with high fever for several days. Her mother was alarmed by the curious appearance of the urine. She stated that it had "a dark mahogany color and was thick like coffee." No edema was noticed. As she recovered from this infection the urine regained its usual color and no further attention was paid to any possible kidney disease until 1922 when she was taken to a doctor because her legs had become swollen. She had been listless for some time and too tired to play. The urine seemed to the mother to be normal but after examining a specimen the doctor said the girl had nephritis. For six weeks she was kept in bed on a milk diet, and although at the end of that period the edema had gone the mother was advised to leave Colorado where they were then living and to take her daughter to California. There the child's health improved and there was no return of the edema until 1923 when it reappeared for a short time only.

She was first seen in August 1925 when she was referred for investigation because a large amount of albumin has been found in the urine. During the preceding two years although very little time had been lost from school she had not been strong and had been obliged to abstain from most of the school games. During the preceding few months she had vomited on several occasions without any good reason and with only slight and transient nausea, and she had also been troubled by rather severe cramps in the muscles of her legs. On physical examination no arteriosclerosis was detected and even the retinal arteries were passed as normal. But the systolic blood pressure was 140 and the diastolic 100, though the heart could not with any certainty be said to be enlarged. There was no anemia. After abstention from fluids during the day the twelve hour night urine had a volume of 460 c.c. and a specific gravity of 1.014. It contained 4050 mg. of protein. The number of casts was 3,750,000. They were nearly all faint hyaline casts. No blood casts were seen but a few renal failure casts were found. The number of red blood cells in twelve hours was 7,180,000. The urea ratio test indicated that only 13 per cent of the normal amount of renal tissue was functioning. The blood urea concentration was 82 mg. per 100 c.c. The subsequent course is shown in Table XXXII.

Table XXXII

Date	Casts, per 12 hrs.	R.B.C., per 12 hrs.	Protein, mg. per 12 hrs.	Volume, per 12 hrs.	Sp. gr.	Blood urea, mg. per 100 c.c.	Blood pressure	
							Systolic	Diastolic
1925 Aug. 8	....	....	.....	...	.....	82		
Aug. 18	3,750,000	7,180,000	4,050	460	1.014	...	140	100
Aug. 29	....	....	.....	...	.....	...	130	95
Oct. 17	....	....	.....	...	.....	117	120	95
Dec. 16	....	....	.....	...	.....	...	125	80
1926 Feb. 6	573,000	19,500,000	5,759	635	1.013	...	140	100
Mar. 13	360,000	18,900,000	5,760	750	1.013	227		
May 24	Died							

On a diet containing 40 gm. of protein, a low sodium content and 2000 calories the vomiting ceased, she had no more cramps and was able to enjoy her school work. But in October the blood urea concentration had risen to 117 mg. per 100 c.c. and by February 1926 all the casts were renal failure casts. She was last seen in March 1926. The blood urea concentration was 227 mg. per 100 c.c. and the urine even after abstention from fluids had a volume of 750 c.c. per 12 hours and a specific gravity of 1.013. In spite of these ominous findings the patient looked well and had not missed a day from school for months. In May her physician wrote that she was dead. Ten days before the end she had a severe epistaxis. She stayed in bed after this, and grew gradually more drowsy until she died in deep coma.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained at autopsy. They were not greatly reduced in size, measuring 11 × 5 × 4 cm. The capsule stripped with some difficulty, leaving a surface studded with fine granular scars of a greyish color. On the cut surface there was some reduction in the breadth of the cortex but no other significant lesions. The arteries were apparently normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all the glomeruli are involved. The lesion consists of the later stages of an active glomerulitis. In some instances the glomerular tuft is enlarged with more or less fibrous exudate and crescents fill the capsular space. The majority of the tufts however are more or less completely fibrosed and the capillaries are obliterated. Around these there is very definite periglomerular thickening.

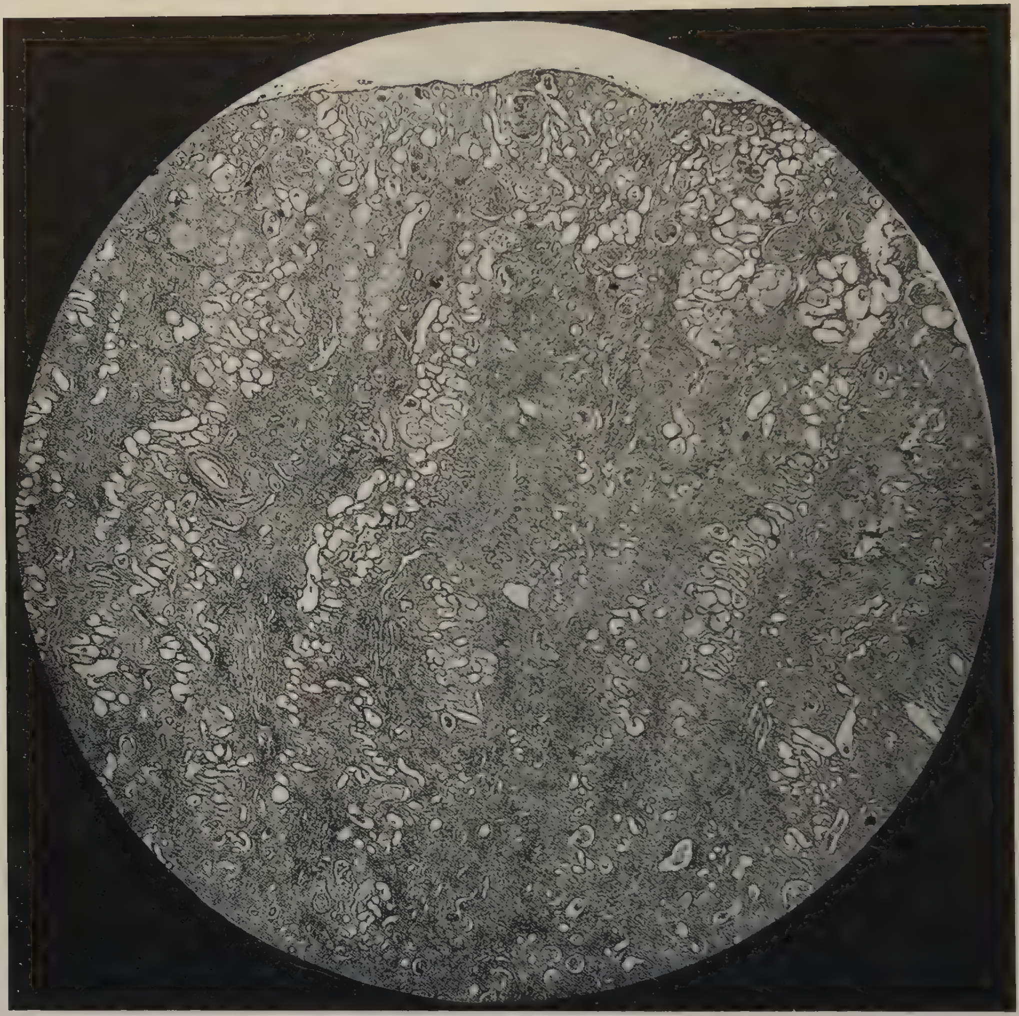

PLATE XXXIV A

The extreme irregular inflammatory proliferation of the interstitial tissue has produced irregular areas of tubular collapse which contrast with groups of tubules which are dilated. The glomeruli at this magnification are almost completely invisible on account of their fibrosis. The granular surface of the kidney may be observed.

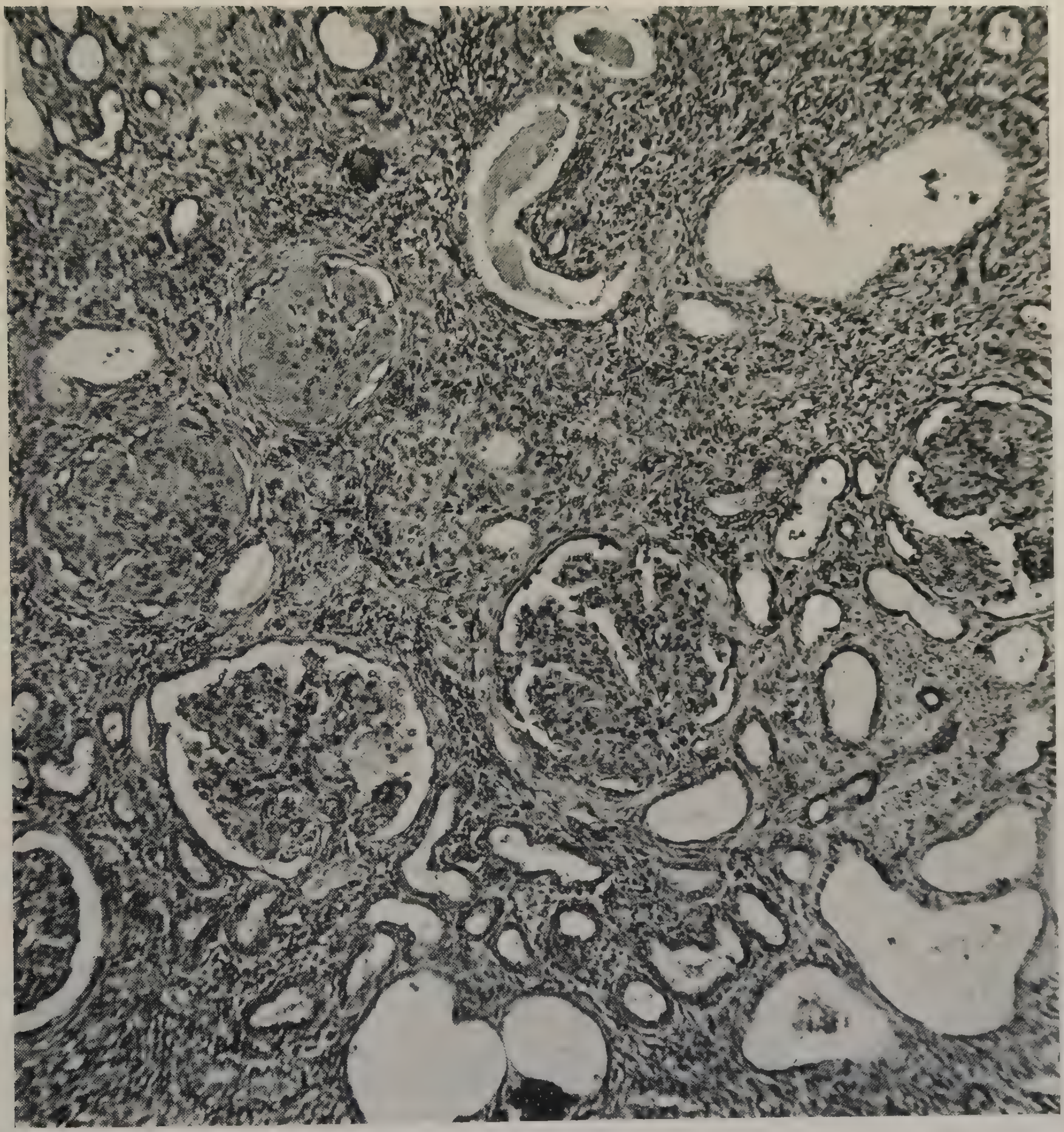

Plate XXXIV b

Various stages of the inflammation in the glomerular tufts are seen. In the left upper portion of the figure are two glomeruli which are completely fibrous. An irregular distortion of the tubules is evident, an effect of fibrosis in the interstitial tissue.

Tubules. The greater number of the convoluted tubules in the cortex are destroyed by the interstitial lesions. They consist of compressed, distorted columns of atrophied epithelial cells with little or no lumen. Scattered through the cortex are isolated groups of convoluted tubules which are markedly dilated and filled with coagulated homogeneous material and leucocytes. The epithelium of these tubules is somewhat swollen and granular and occasionally a group is found which shows fatty degeneration. The straight tubules, especially the large collecting tubules, contain many poorly formed large renal failure casts. A few smaller hyaline and granular casts are also found.

Interstitial Tissue. There is an extreme involvement of the interstitial tissue consisting of a marked increase in fibrous connective tissue and a diffuse round cell infiltration. In the cortex this has replaced the greater part of the tubular tissue. Scattered throughout the more severely involved areas are considerable collections of fat droplets enclosed in large swollen connective tissue cells.

Arteries. There is no significant lesion in the larger arteries.

SUMMARY

The kidneys show late stages of a glomerulitis, extensive destruction of the cortical tissue by cellular infiltration and fibrosis, and moderate epithelial degeneration with many large renal failure casts. The arteries are essentially normal.

CASE XXXV

Ernest G. Aged twenty-eight.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown.

Etiology. No information.

Course. The patient came on January 21, 1925, saying that he had had headaches for a month and had recently been vomiting without any obvious reason. His principal complaint, however, was dimness of vision which he had noted one week before.

His past history was free from any note of serious illness but he had suffered from frequent sore throat. He had had scarlet fever when a child but there was no reason to suppose that there had been any nephritis.

The blood pressure was 190 systolic and 140 diastolic but there was no noteworthy thickening of the radial or brachial arteries. There was a well-developed neuroretinitis. The heart did not seem to be enlarged and this impression was confirmed by *x*-ray examination. The hemoglobin was 75 per cent. There was no edema.

A concentration test had a volume of 873 c.c. per twelve hours with a specific gravity of 1.009. The number of red blood cells was 113,000,000 per twelve hours and there were 5,000,000 white blood cells and epithelial cells. All of the casts (27,000 per twelve hours) were of the renal failure type. Several other tests gave similar results. The rate of protein excretion varied between 860 and 1980 mg. per twelve hours.

There was a slight improvement in the retinitis. The blood urea concentration which was 117 mg. per 100 c.c. on January 27, fell to 81 mg. on February 16 and the blood pressure fell to 160 systolic and 95 diastolic. Thereafter, however, the symptoms of uremia recurred and by March 24 the blood urea concentration had risen to 179 mg. per 100 c.c. The patient died on April 8 of typical uremia with a blood urea concentration of 400 per 100 c.c.

PATHOLOGICAL OBSERVATIONS

The kidneys and spleen only could be examined after death. The kidneys were small, averaging 9 × 4 × 3 cm. The capsule stripped with some difficulty leaving a dark red granular surface. The cut surface showed a fibrosis and reduction of the cortex. The renal artery was somewhat thickened. The spleen was normal to gross examination, and microscopical examination showed its arteries to be normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Only a few glomeruli, 2 or 3 to a low powdered field, remain in a condition at all resembling their normal structure. Their tufts are either shrunken by fibrosis or enlarged by the development of new fibrous tissue in them. In both

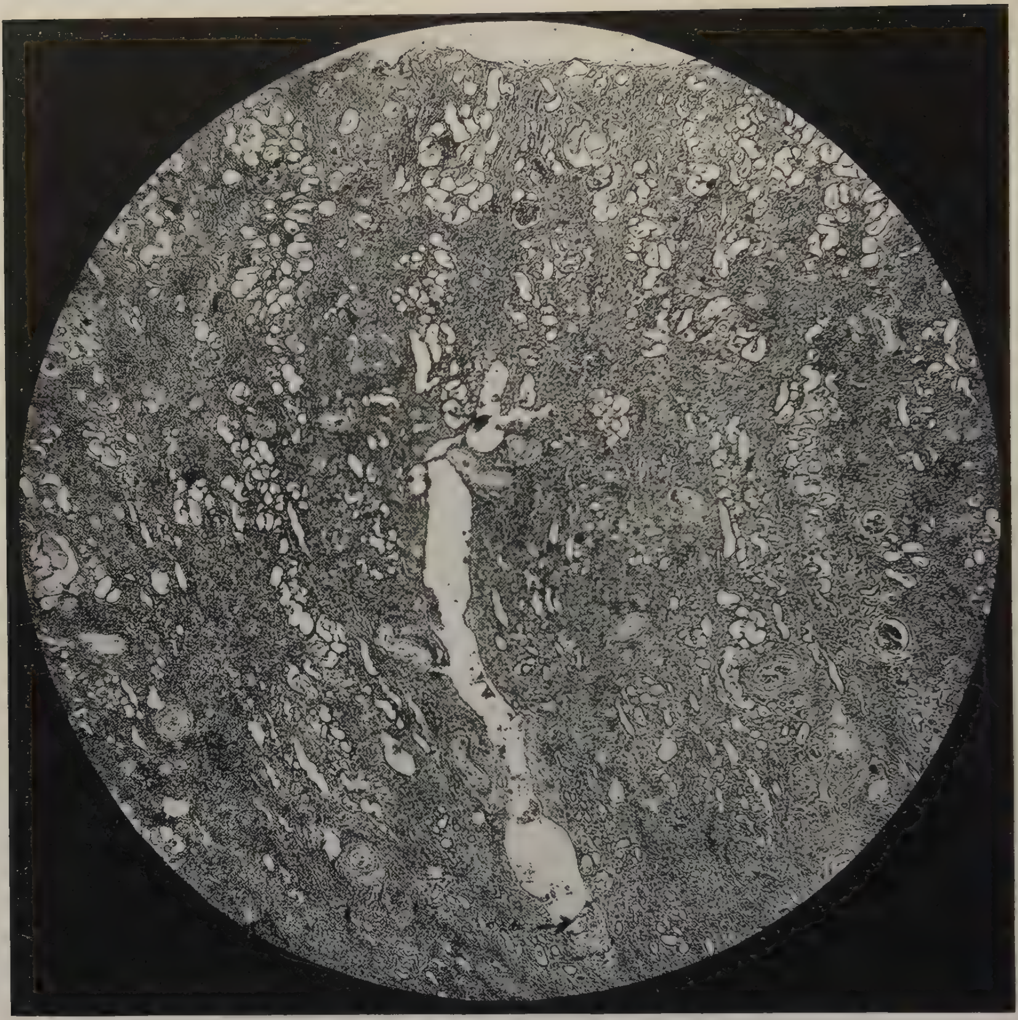

PLATE XXXV A

The inflammatory proliferation of the interstitial tissue is still quite cellular, scattered areas of round cell infiltration appearing throughout the section. The tubules are either compressed or dilated and very few glomeruli can be made out. Some sclerotic arteries in the center of the section at the end of the greatly dilated vein can be seen. The granulation of the surface is apparent.

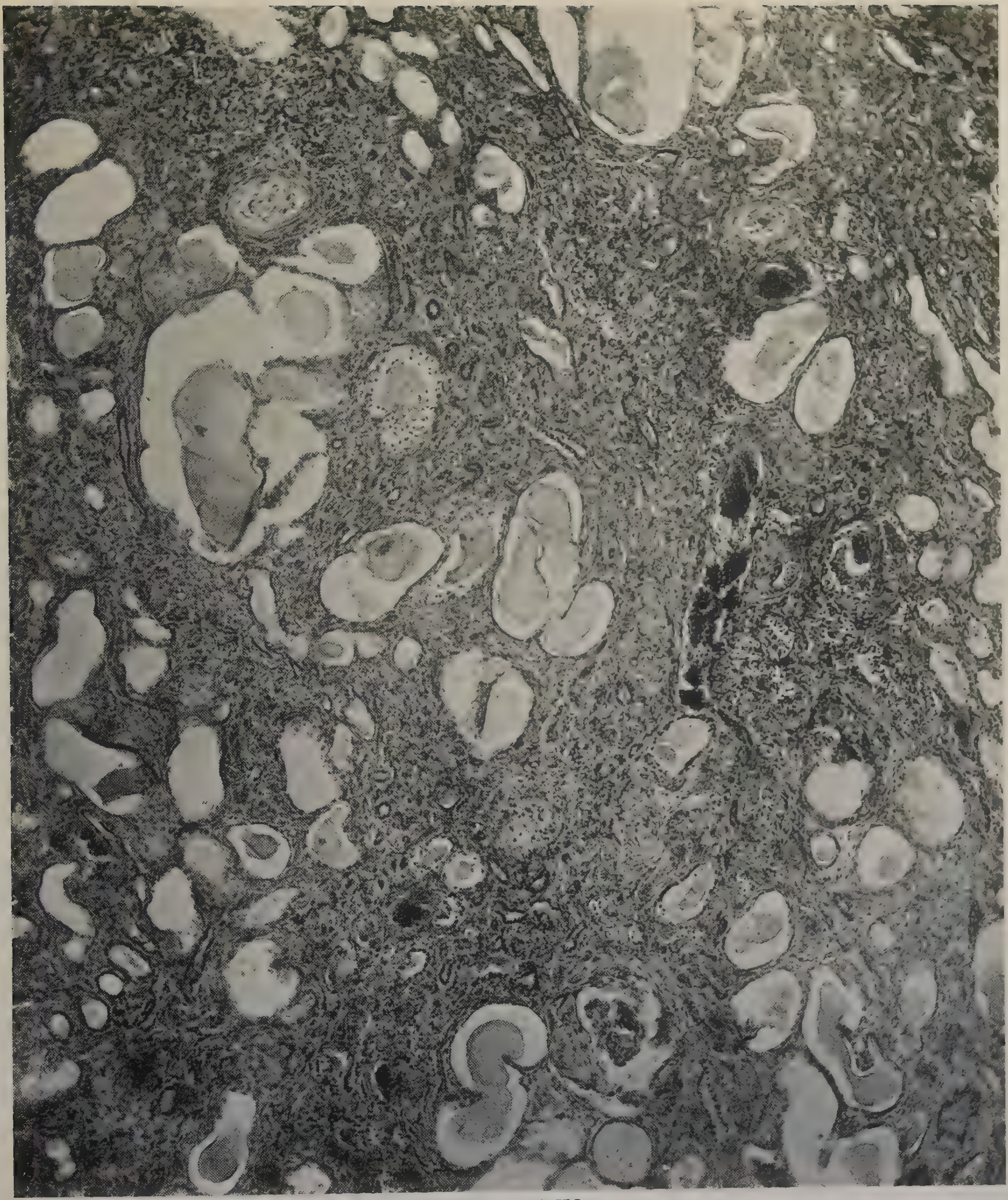

PLATE XXXV B

The glomeruli are almost completely destroyed. The remains of one can be made out at the lower middle portion of the plate. Tubular dilatation and the production of cyst-like cavities filled with colloid alternate with areas of tubular obliteration. A blood cast can be seen in the right middle portion in the plate.

cases there are many leucocytes, mostly mononuclear but occasionally polymorphonuclears, present. Bowman's space is obliterated by fibrous adhesions, or filled with organized crescents. The great majority of the glomeruli exist only as small hyaline nodules.

Tubules. The convoluted tubules of the cortex are either compressed and atrophied or, in the areas where the interstitial proliferation is less marked, dilated to form cystic spaces which are lined with flattened cells and filled with hyaline colloid-like material. Very few of these large tubules show any hypertrophy of their epithelium. The lumens of some of the straight tubules contain hyaline or granular casts, and there are many large renal failure casts in the collecting tubules.

Interstitial Tissue. There is a marked increase in the amount of fibrous interstitial tissue irregularly scattered throughout the cortex. There is a heavy leucocytic infiltration, the cells being chiefly mononuclears. Deep retracted scars are found where the fibrous tissue reaches the free surface and the whole architecture of the cortex is destroyed by its irregular distribution.

Arteries. All of the arcuate arteries and the smaller interlobular arteries show a marked proliferation of the fibrous tissue in their intima and walls.

SUMMARY

The kidneys show a late stage of chronic inflammatory processes in their glomeruli and interstitial tissue. The tubules have suffered by replacement with scar tissue. There is a marked sclerosis of the arteries. Judging from the normal arteries in the spleen they were not part of a general arteriosclerosis.

CASE XXXVI

Verna G. Aged twenty-one.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Seven years?

Etiology. Tonsillitis.

Course. When fifteen years old she had a severe tonsillitis. She had not grown since then and was not entirely strong and well although no disabling symptoms presented themselves, until five months before her death in uremia. At that time she developed gout in her right metacarpophalangeal joint. It was found then that the urine was dilute and contained much protein and only renal failure casts. The blood pressure was at very high levels and the blood urea concentration 138 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

Although this girl was twenty-one years old when she was first seen she would have passed for fifteen. She said that two weeks previously she had suffered from a severe pain in her right big toe. There was redness and extreme tenderness over the joint. She had just entirely recovered. This arthritis had led to the examination of the urine and she had been sent for investigation because a heavy proteinuria had been discovered.

There was a marked anemia and slight pitting edema of the legs. Several bruises due to slight traumata were present. The reflexes were extremely active. The blood pressure was 220 systolic and 140 diastolic with a pulse rate of 116. There was obvious enlargement of the heart to the left but no evidences of circulatory failure. There were no retinal hemorrhages or exudate.

Until the appearance of what presumably had been an attack of gout there had been no suspicion of any renal disease, although her sister had been under observation for many years for a hemorrhagic nephritis in the latent stage. It was of course known that she was not very well, and her subnormal health was definitely connected in the mind of her mother with a severe tonsillitis which had kept her in bed for three weeks when she was fifteen years old. It is certain at least that she had grown neither in height nor in weight since that illness.

A concentration test gave a volume of 935 c.c. per twelve hours with a specific gravity of 1.010. There were 113,000 casts, all of them renal failure casts. The number of red blood cells was 1,800,000 and there were 8,800,000 white blood and epithelial cells. Most of these were probably renal cells. There was no evidence of fatty degeneration. The rate of protein excretion was 2750 mg. per twelve hours. The blood urea concentration was 138 mg. per 100 c.c. Subsequent examinations failed to show any casts but there were from 1,000,000 to 3,500,000 red blood cells and from 8,000,000 to 21,000,000 white blood cells and epithelial cells.

During the next four months she was able to go on with her school work but there was a gradually progressive weakness. The blood urea concentration mounted

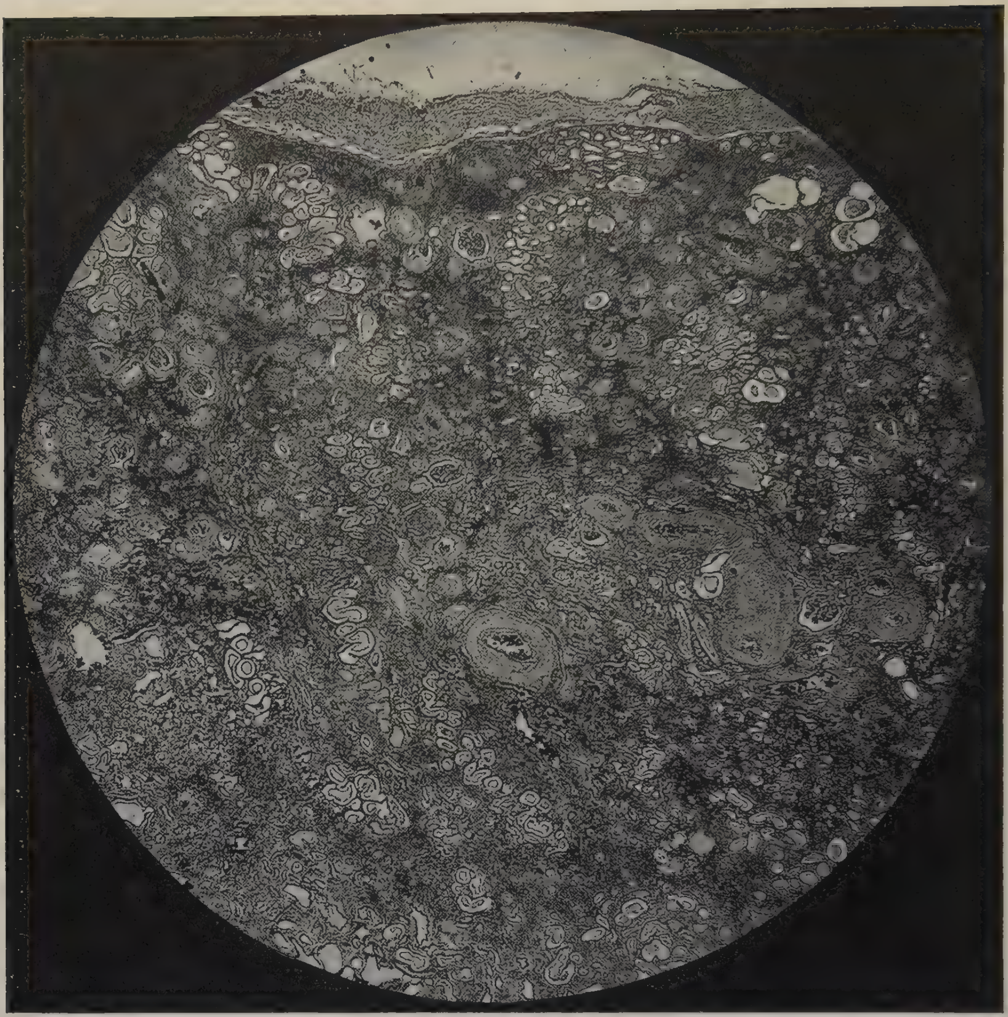

Plate XXXVI a

There is a markedly patchy inflammatory proliferation of the interstitial tissue with dark areas of intense round cell infiltration. Tubules and glomeruli are destroyed and the arteries show marked sclerosis.

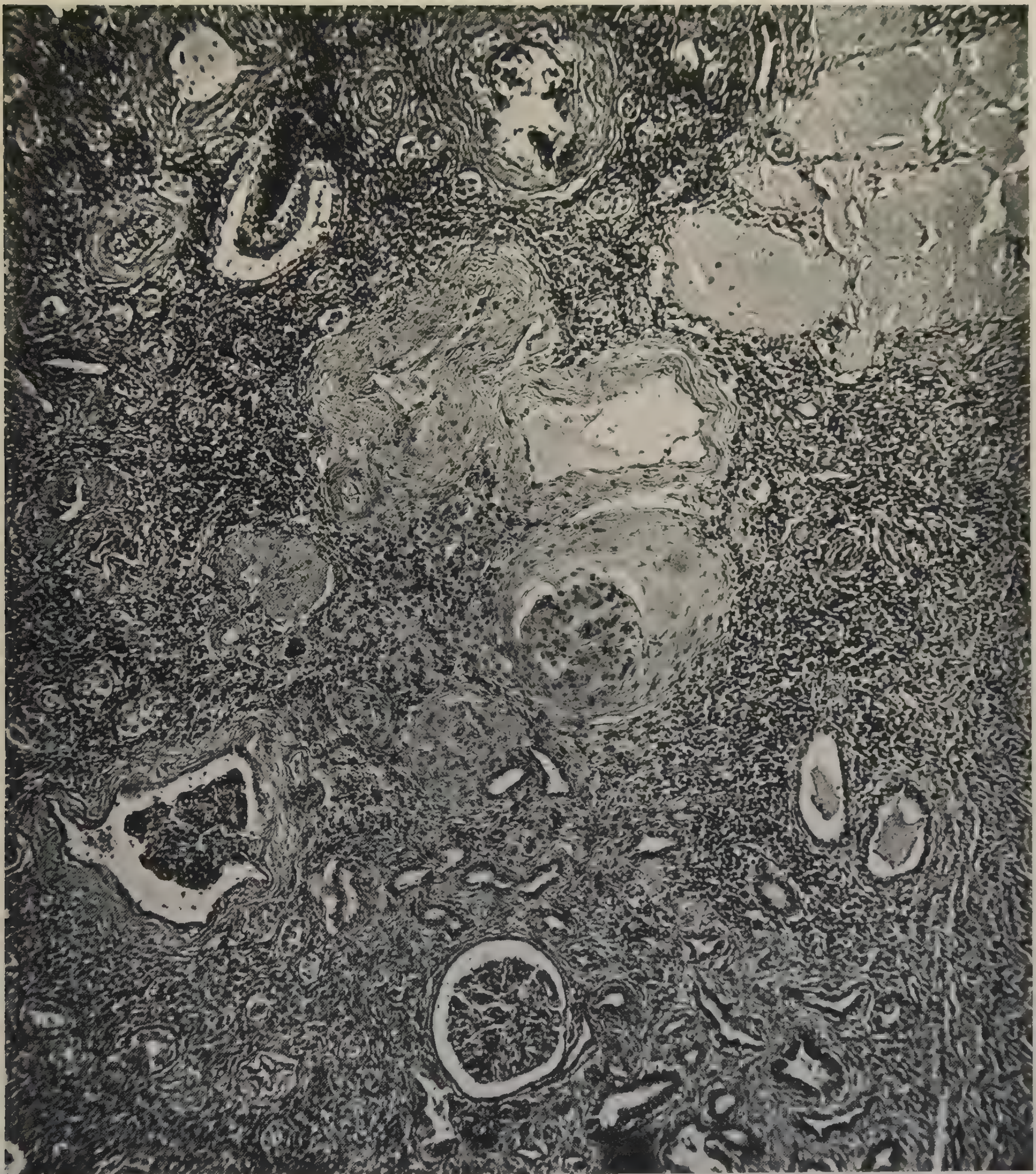

Plate XXXVI b

Extreme fibrosis and leucocytic infiltration of the interstitial tissue has almost completely obliterated the tubules. The glomeruli are surrounded by fibrous rings and their tufts are more or less compressed. Note the greatly thickened arterioles.

slowly but steadily until it reached the level of 383 mg. per 100 c.c. Vomiting then set in, pericarditis developed, and there were signs of consolidation at the right lower lobe of the lung. She died in coma a few days later.

PATHOLOGICAL OBSERVATIONS

At autopsy the heart was found to be one and one-half times its normal size. In the coronaries and aorta were many yellow plaques. In the serosa of the jejunum was a white nodule 6 mm. in diameter which was filled with white chalky urates. The kidneys averaged 9 × 2 × 1.25 cm. in measurement. Their capsules were firmly adherent, stripping with difficulty and leaving an irregular scarred finely granular surface. The cut section of both showed a marked reduction of the cortex and in the medulla were streaks of white chalky deposit (urates). The renal arteries were very prominent and thickened. As terminal infections there were present an acute pericarditis and a bronchopneumonia.

MICROSCOPICAL EXAMINATION

Glomeruli. Some of the glomeruli, about one-quarter the total number, have maintained to a certain extent their normal structure. They are increased in size and the capillaries of their tufts are patent. The greater number, however, about half the total, show varying degrees of fibrosis. In some, remnants of the compressed tuft can still be distinguished, but in most the whole structure is reduced to a hyaline nodule of collagen. Around many of those which are not yet completely destroyed there is a dense periglomerular fibrous thickening of the capsule. In still other tufts, comprising roughly the final quarter, there are definite evidences of inflammatory processes. The tufts are infiltrated with leucocytes, more or less fibrosed and there are adhesions which obliterate Bowman's space. No collection of inflammatory exudate such as fibrin, red blood cells or polymorphonuclear leucocytes are found in the space however, nor glomerular crescent formation.

Tubules. Throughout those areas of the cortex where there is extensive proliferation of the interstitial tissue the convoluted tubules are markedly affected. Many are completely collapsed, existing as small clumps of atrophied cells; in others the lumen of the tubule still persists and is lined by a narrow dark-staining distorted epithelium. In the regions where the fibrosis is less dense the tubules are of normal size or even dilated to a greater diameter. They are lined with either an atrophied or atypically regenerated epithelium and their lumens contain debris or hyaline or granular casts. In some of these casts are many polymorphonuclear leucocytes. No blood casts are found, but in the collecting tubules are many poorly consolidated large renal failure casts. Active degenerative processes are not extensive in any of the tubular epithelium, though cells may be found which show cloudy swelling.

Interstitial Tissue. There is an extensive irregular patchy inflammatory proliferation of the interstitial tissue throughout the cortex. In the new-formed connective tissue there is a marked development of collagen and a heavy infiltration with leucocytes, these mostly mononuclears but some also of polymorphonuclear type. In the medulla between the straight tubules are narrow slit-like spaces, now empty, which contained the urate deposits. About them there is a definite increase in the degree of leucocytic infiltration.

Arteries. The larger arcuate arteries and interlobular branches show a very marked fibrous thickening of their intima. The sclerosis is even more severe in the smaller arterioles in the cortex, these being almost occluded by the thickening of their walls.

SUMMARY

The kidney shows an old inflammatory involvement of the glomeruli with extensive inflammatory fibrosis of the cortex and destruction of the tubular elements. There is also an extreme sclerosis of the arteries and gouty deposits in the medulla. It is of interest that the clinical history indicates two etiological factors in this case, tonsillitis, from which event the renal disturbance dated, and a later complication of gout.

Case xxxvii

Margaret G. Aged twenty-six.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Five and a half years. Observed during the last three and a quarter years.

Etiology. No information.

Course. The initial stage may have occurred following an undiagnosed fever in April 1922. In August of that year the diagnosis of Bright's disease was made. She was first seen in August 1925. There was then a pronounced albuminuria but the intensity of the lesion was slight since there were only a few million red blood cells per twelve hours. The extent of the lesion however was considerable. In September, 1925, 34 per cent of the normal amount of functioning renal tissue was present. During the next year and a half the proportion of renal failure casts increased and the amount of functioning tissue fell to 17 per cent of normal. Thereafter there was a slow but steady increase in the blood urea concentration and the patient died of uremia three and a quarter years from the time at which she was first seen, and five and a half years from the time at which the lesion probably had its origin.

RELEVANT CLINICAL DETAILS

In April 1922 she was in bed for a week with fever and a dull pain in the left lumbar region in the midaxillary line. No doctor was called. In August of that year there was a recurrence of this pain. It was supposed that she might have a renal stone but after a cystoscopic examination had been made she was told that "both of her kidneys were inflamed" and that she must take a special diet. The pain soon went and she felt entirely well.

She was first seen in August 1924. She looked very strong and well and came not on account of any symptoms but because the albuminuria found two years before was still present. No evidence of cardiac enlargement was found. The blood pressure was 130 systolic and 100 diastolic. The retinal arteries were slightly tortuous and there were varicosities on some of the veins where they were crossed by arteries. There was no anemia. In September 1924 the amount of still functioning renal tissue was only 34 per cent of normal, but the lesion though so extensive gave evidence of a very low grade of intensity. There were no signs of any degenerative process for all through 1924 the number of white blood cells and epithelial cells never went appreciably above 1,000,000, nor was there any very active inflammatory element since the highest red blood cell count was 5,700,000 per twelve hours. The urine tended to be dilate and even after abstention from fluids, casts were not always found and then only in small numbers. In November 1924 the rate of cast excretion was 950 per twelve hours, and 20 per cent of these were of the renal failure type. The rate of protein excretion varied between 980 and 2400 mg. per twelve hours, quantities larger than are found in uncomplicated arteriosclerosis but much less than those observed in the active stages of hemorrhagic nephritis. The conclusion was reached that the patient was very slowly passing from the latent to the terminal stage.

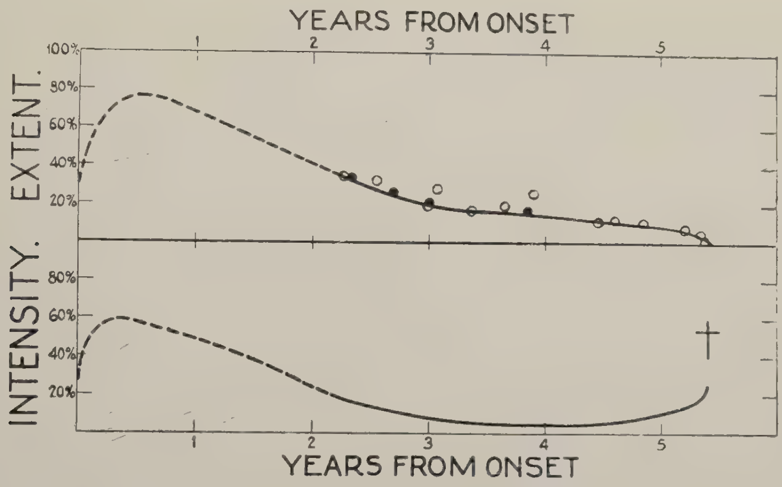

FIG. 21. Upper curve shows changes in amount of functioning renal tissue. Black dots represent actual determinations. Circles are estimates based on blood urea concentrations. Lower curve indicates intensity of renal lesion as judged by sediment counts. In both cases broken part of curves is hypothetical and gives probable general course from commencement of process until patient came under observation.

The gradual but steady decrease in the amount of renal tissue from August 1924 until her death of uremia in November 1927 is shown in Figure 21. The results obtained in the concentration tests are given in Table XXXIII.

In dramatic contrast to the slow but relentless progress of the disease was the happy carefree life of the patient up to within a month of her death. During these three years she was continuously at work for eight hours a day, and during that time was free from all subjective symptoms. She married and twice became pregnant, and there was some difficulty in obtaining permission to terminate the pregnancies. She even obtained insurance because she looked and felt so well and the examining agent apparently did not believe that the albuminuria could possibly have any serious significance. The blood pressure did not reach definitely abnormal levels until September 1927 at about the time when exudate and hemorrhages were first seen in the retinae. In October 1927 vomiting without nausea started. She entered the hospital because she believed she had again become pregnant. But the blood urea concentration was 445 mg. per 100 c.c. and rapidly rose to 625. A slight general anasarca developed with petechial hemorrhages into the skin. She became lethargic and finally comatose and died on November 7, 1927.

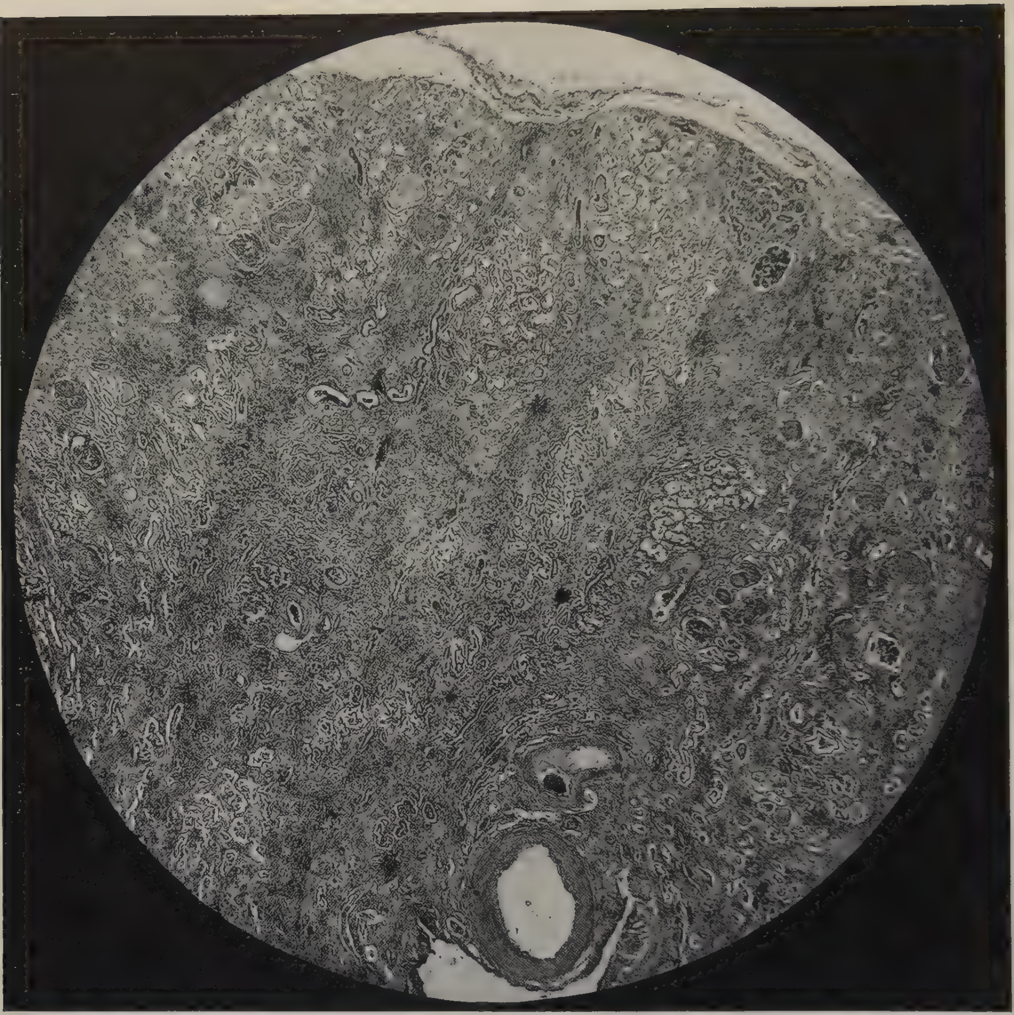

Plate XXXVII a

The extreme fibrosis of the interstitial tissue has destroyed the greater number of the tubules though irregular clusters remain, much hypertrophied. An occasional large glomerulus can be made out. Near the sclerotic arteries in the lower part of the section a portion of a greatly dilated vein is visible.

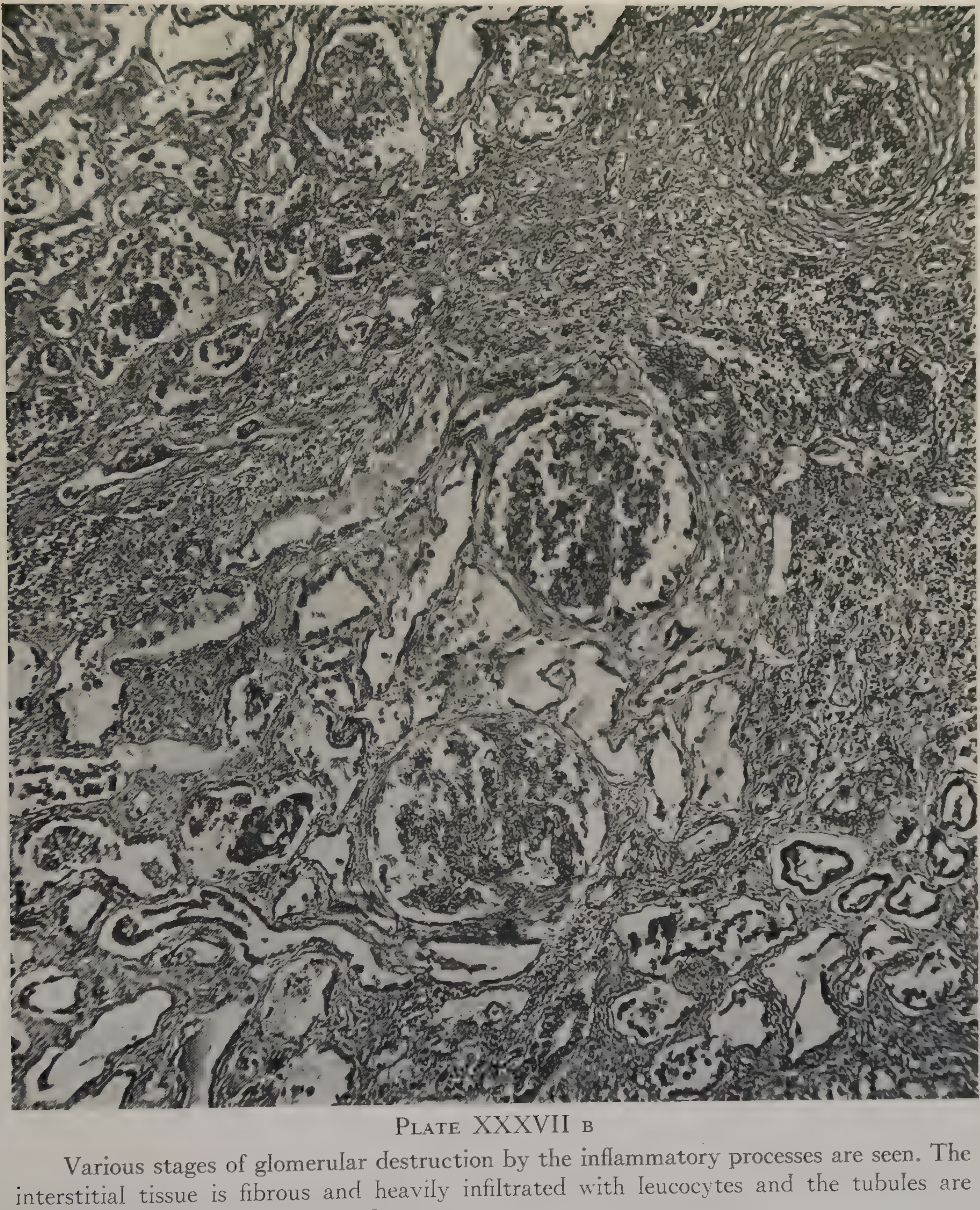

PLATE XXXVII B

Various stages of glomerular destruction by the inflammatory processes are seen. The interstitial tissue is fibrous and heavily infiltrated with leucocytes and the tubules are collapsed or compressed as a result.

TABLE XXXIII

TWELVE HOUR RATES OF EXCRETION AFTER ABSTENTION FROM FLUIDS

Date	No. of casts	No. of R.B.C.	No. of W. & EP. C.	Protein mg.	Vol. c.c.	Sp. gr.	Blood urea, mg. per 100 c.c.
1924 Aug.	1,960	5,700,000	181,000	2,400	852	1.016	52
Sept.	2,580	3,300,000	308,000	1,530	459	1.029	
Nov.	4,950	4,240,000	1,100,000	2,080	445	1.019	55
1925 Jan.	5,890	268,000	965,000	910	169	1.019	
June.	0	4,570,000	....	1,350	427	1.014	58
Oct.	5,210	6,680,000	1,580,000	1,800	625	1.015	82
1926 Jan.	0	10,000,000	8,900,000	1,355	448	1.013	77
Feb.	0	5,000,000	....	1,218	470	1.014	81
July.	0	463,000	....	1,052	330	1.016	95
Oct.	0	1,150,000	....	900	...	1.014	109
1927 Jan.	0	3,950,000	....	746	274	1.015	95
Sept.	6,500	3,000,000	....	862	292	1.011	194
Oct.	0	2,450,000	9,200,000	2,208	395	1.012	345
Oct.	11,000	4,500,000	5,600,000	1,500	248	1.016	445

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a secondary anemia and a terminal broncho-pneumonia. The kidneys were small, averaging 8 × 4 × 2.5 cm. The capsule stripped with considerable difficulty, leaving a rough granular surface of a purplish red color. The cut surface showed indistinct markings and a reduction in the breadth of the cortex. The renal arteries were somewhat thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. In each low power field of the cortex two or three glomeruli can be found which still retain to some degree their usual structure. They are as a rule increased in size. The tuft is infiltrated with a moderate number of leucocytes, but the capillaries are in the most part compressed by the development of fibrous connective tissue. Bowman's space is more or less obliterated by the development of fibrous adhesions. The remaining glomeruli show increasing degrees of a similar infiltration and fibrosis, most of them being reduced to masses of purely hyaline collagen.

Tubules. In large areas of the cortex the tubules are almost entirely destroyed by the proliferation of the interstitial tissue. Small groups of atrophied cells, cross sections of solid cords, or distorted channels with irregular lumens are scattered through the fibrous tissue. In this dense tissue are small nests of tubules, lying as a rule just beneath the free surface of the cortex, which are better preserved and which are either dilated or hypertrophied. In some of these active degenerative processes such as cloudy swelling and fatty degeneration are present. In the collecting tubules are many large renal failure casts.

Interstitial Tissue. There is an extreme proliferation of the interstitial tissue throughout the cortex. This tissue is very fibrous, almost hyaline in large areas and scattered through it is a diffuse infiltration with leucocytes, the majority of which are mononuclears. The retraction of this scar tissue is so general throughout the cortex that the commonly seen locally retracted scars are not prominent.

Arteries. All the arteries, both arcuate and smaller interlobular branches, show an irregular proliferation of their intima.

SUMMARY

The kidneys show a very late stage of chronic inflammatory process affecting the glomeruli and interstitial tissue. There is widespread destruction of the architecture of the cortex, the tubules having almost disappeared in places. The arteries show a marked sclerosis.

CASE XXXVIII

Elizabeth G. Aged twenty-seven.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown.

Etiology. No information.

Course. There was no history in this case of any initial stage nor any knowledge of renal disease. She came complaining of vomiting and anemia and died nineteen days later of uremia.

RELEVANT CLINICAL DETAILS

The patient stated that she had not been quite well for a year and it had been noted that she was growing pale. But no other symptoms developed until about Christmas 1924 when she began to have an occasional vomiting which was unaccompanied by pain or more than transient nausea and which had no constant relation to the taking of food. This vomiting became more frequent and soon occurred at least once a day. At about the same time she became noticeably short of breath on exertion and there was a slight but definite swelling of the ankles at night, and under her eyes in the morning. There was no history of any serious illness in the past. As a child she had had a series of attacks of sore throat. The last of these attacks had occurred seven years ago and had been complicated by the formation of a tonsillar abscess.

She was first seen on April 7, 1925. The skin was yellow and the lips pale. The red blood cells numbered 2,310,000 per cubic millimeter. There was no edema but she had been in bed for a week. The hands were trembling, all the reflexes were markedly exaggerated and there was slight exophthalmos. The retinal arteries showed typical arteriosclerotic changes where they were not obscured by patches of fresh exudate. Yet there was no recognizable thickening of the radial or brachial arteries and the heart did not seem to be enlarged. The blood pressure was 130 systolic and 80 diastolic. This normal diastolic pressure is interesting though not very unusual. It was a terminal phenomenon for in this case several previous measurements had shown a hypertension. On February 17 the systolic pressure was 195 and the diastolic 130, and on March 31, 190 and 120.

The blood urea concentration was 370 mg. per 100 c.c. on April 7, on the fourteenth it was 485, on the sixteenth 551, and on April 23, the day of death, it had risen to 631 mg. per 100 c.c.

The urine was constantly of low specific gravity. No casts were seen. There was a macroscopic pyuria. The rate of protein excretion was 1330 mg. per twelve hours. The pyuria had not been noted before April 7 and it seems likely that the pyelitis which was found at the postmortem examination was a terminal event.

PATHOLOGICAL OBSERVATIONS

At autopsy the heart was found to be one and one-half times its normal size, though its valves were normal. No other significant lesions were found in any of the other organs. The kidneys were small averaging 6 × 3 × 1.5 cm. Their capsules stripped with great difficulty, leaving a roughly granular surface. The cut surface showed a marked narrowing of the cortex. The renal arteries were apparently normal.

MICROSCOPICAL EXAMINATION

Glomeruli. The glomeruli are reduced in number to such a degree that in a low power field only two or three can be found which maintain any resemblance to their normal structure. Even these have large fibrous tufts which are heavily infiltrated with leucocytes, both mononuclear and polymorphonuclear, and Bowman's space is filled with fibrous adhesions. Some of these glomeruli show on the other hand a marked cystic dilatation of the space with a compressed tuft. The remaining glomeruli are small and fibrous, and a great number are reduced to small hyaline masses of collagen.

Tubules. In large areas the tubules are practically completely destroyed by the dense proliferation of the interstitial tissue. Small clusters of atrophic epithelial cells remain as irregular channels lined with compressed cells. On the other hand alternating with these areas of tubular destruction are groups of tubules which are definitely hypertrophied. Such are lined with a thick epithelium of normal type, whose lumens are filled with granular material. Other of the tubules in these regions show a marked dilatation of their lumen and are filled with colloid-like material. The epithelium of such tubules is markedly atrophied and flattened. In the collecting tubules are many large renal failure casts.

Interstitial Tissue. Large areas of the cortex have been almost completely replaced by dense fibrous connective tissue which in places is almost hyaline in appearance. In this tissue is a diffuse infiltration with leucocytes that in some areas is extremely dense. Polymorphonuclears are present in these but are few in number. This increase in connective tissue is very irregular throughout the cortex and leaves some areas relatively free. In these are found the large tubules and glomeruli previously described.

The pelvis of the kidney contains pus and desquamated epithelial cells. In the tissues of the medulla lying near the pelvis there is a heavy infiltration with polymorphonuclear leucocytes and some of the collecting tubules are filled with these cells.

Arteries. All of the arteries, both arcuate and interlobular, show a marked fibrous thickening of the intima.

SUMMARY

There is present an old chronic inflammatory process involving the glomeruli and interstitial tissue. The tubules are compressed by these proliferative processes and the arteries show a sclerosis. A chronic suppurative pyelitis is also present.

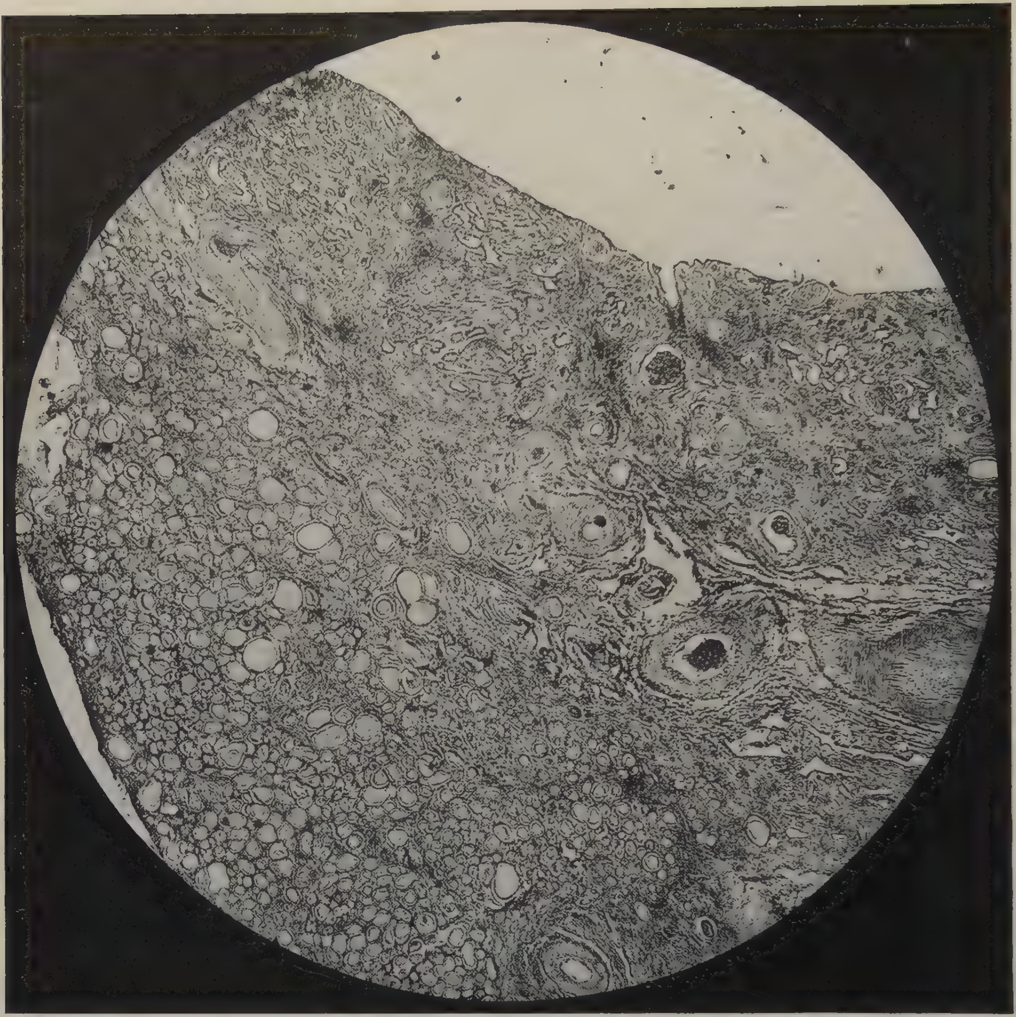

Plate XXXVIII a

There is an extreme distortion of the architecture of the kidney as a result of the inflammatory sclerosis in the interstitial tissue. The tubules are dilated and filled with colloid in one part of the section and compressed and atrophied in the other. Only an occasional glomerulus can be made out. Several branches of the renal artery show an extreme sclerosis.

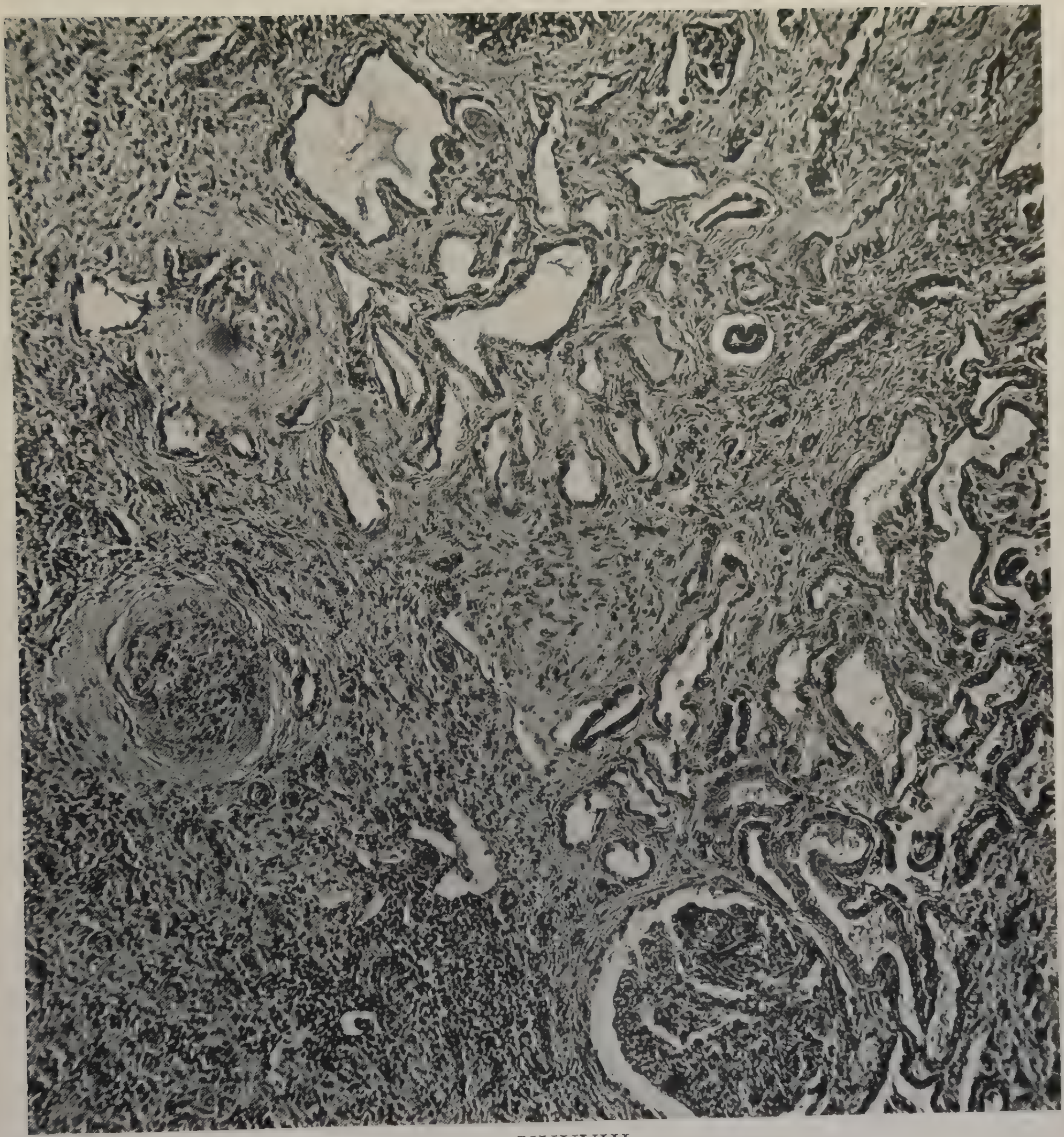

Plate XXXVIII b

The glomeruli in the left part of the section are almost completely fibrous. Heavy round cell infiltration and connective tissue proliferation in the interstitial tissue has produced the usual distortion of the tubules.

CASE XXXIX

Charles H.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown.

Etiology. No information.

Course. Retinitis and hypertension were discovered in August 1924. By December 1924 the heart was decompensated, the urine contained only renal failure casts and the blood urea concentration was 196 mg. per 100 c.c. After a temporary recovery of cardiac capacity he is reported to have died of uremia in April 1925.

RELEVANT CLINICAL DETAILS

The patient could not remember that he had ever had any illness of note and was in possession of his accustomed good health when in August 1924 he found that the vision of his right eye had suddenly become blurred. An oculist whom he consulted told him he had retinitis and he learned from the physician to whom he was referred that his blood pressure was too high. However, his vision returned and he continued to feel well until December 7, 1924 when he became markedly dyspneic on exertion and found that his ankles were swollen at night. He was first seen on December 24, 1924. The edema had rapidly extended to above his waist. There was free fluid in the peritoneal cavity. The bases of the lungs were congested and the patient was cyanosed. The heart was markedly enlarged. The average blood pressure was high but the heart was fibrillating. A blood count showed that there were 3,760,000 red blood cells per cubic millimeter and 64 per cent of hemoglobin.

On December 24 a concentration test gave a volume of 776 c.c. with a specific gravity of 1.013. The rate of protein excretion per twelve hours was 1560 mg. There were 340,000 casts and they were all renal failure casts. The number of red blood cells was 2,400,000 and there were 3,640,000 white blood cells and epithelial cells. The blood urea concentration was 196 mg. per 100 c.c.

By January 9, 1925, his circulatory condition was much better, and the blood urea concentration had fallen to 177 mg. per 100 c.c. A concentration test on that day had a volume of 557 c.c., a specific gravity of 1.016 and 1200 mg. of protein in twelve hours. There were 171,000 casts, and of these 8 per cent were hyaline and the remainder renal failure casts. The number of red blood cells had fallen to 780,000 while the white blood cells and epithelial cells numbered 3,680,000 per twelve hours.

By January 30, 1925, although the circulatory improvement was maintained the blood urea concentration had risen to 223 mg. per 100 c.c. and on February 16 it was 263. At this time there was occasional vomiting.

His physician wrote that during March there was a return of edema and that he had had to remove large quantities of ascitic fluid. On April 9, he became very restless and jerky twitching movements began which lasted until his death on April 12, 1925.

PATHOLOGICAL OBSERVATIONS

Only the kidneys could be obtained at autopsy. They were definitely decreased in size, averaging 9 × 4 × 4 cm. The capsule stripped easily, leaving a fairly smooth surface of greyish pink color in which a few scars could be seen. The cut surface showed indistinct markings in the cortex. The renal arteries were somewhat thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. There are a relatively large number of glomeruli, 6 to 8 to a low power field, which maintain approximately their normal structure. The tufts are however infiltrated with leucocytes of both the mononuclear and polymorphonuclear type. The capillaries are compressed by a thickening of the connective tissue of the tuft and Bowman's space shows capsular adhesions. Other glomeruli, about one-fourth the total number, are reduced to hyaline masses of collagen.

Tubules. There is the usual atrophy and distortion of the convoluted tubules throughout the cortex that accompanies a marked proliferation of the interstitial tissue. In some places the tubules are less affected by this process, and here parenchymatous degenerations, both cloudy swelling and fatty degeneration, are to be found. There are some hyaline casts in the straight tubules and in the collecting tubules are many renal failure casts.

Arteries. There is a very marked fibrous thickening of the intima of the larger arcuate arteries and the smaller interlobular branches in the cortex show a marked fibrous thickening of their entire walls.

SUMMARY

The kidneys show an old chronic inflammatory involvement of the glomeruli and interstitial tissue. There is a very marked sclerosis of the arteries.

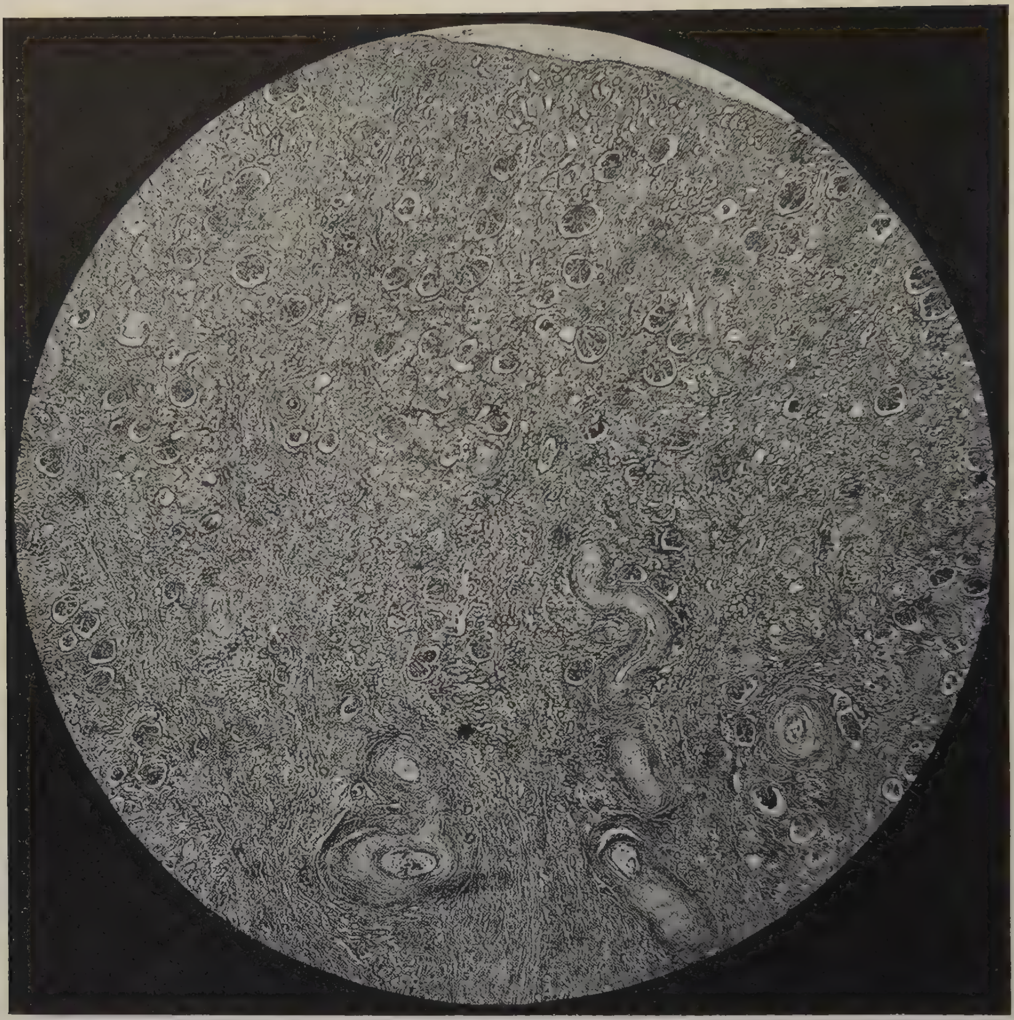

Plate XXXIX a

There is a diffuse and fairly even proliferation of the connective tissue of the framework of the kidney and in it there is a marked round cell infiltration. The tubules are extensively collapsed. Quite a few glomeruli can still be made out in varying stages of inflammatory destruction. There is a marked sclerosis of the arteries.

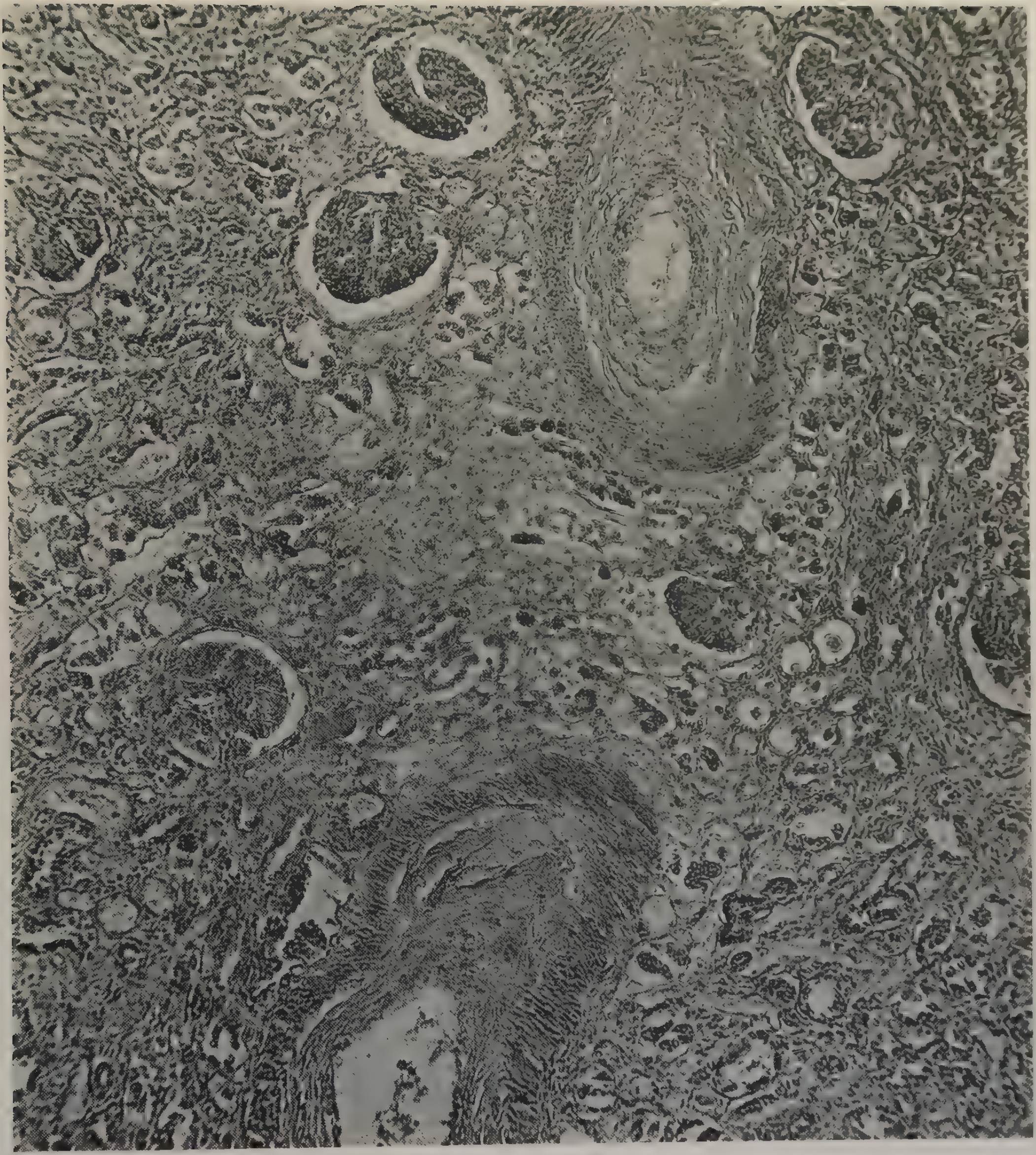

Plate XXXIX b

Two greatly sclerosed arteries are seen. The glomerular tufts are fibrous and shrunken and the scarring in the interstitial tissue has caused marked atrophy of the tubules.

CASE XL

Geneva K. Aged thirty-eight.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown.

Etiology. No information.

Course. This patient had been in supposedly good health, although the history is unreliable, until three months before her death, when she passed through a period of cardiac decompensation from which she recovered under digitalis. She was first seen when she had regained her circulatory equilibrium. She was markedly anemic, the urine was always dilute and contained only renal failure casts and several million red blood cells. The blood urea concentration was 289 mg. per 100 c.c. After a transient improvement she died of uremia.

RELEVANT CLINICAL DETAILS

The patient would give no history but her family had believed that she was in fairly good health until an increasing dyspnea on exertion and advancing edema had forced her to remain in bed. A doctor had not been called until she was almost moribund. The administration of digitalis had been effective and when she was first seen there was little edema left and her respiration was normal. She was markedly anemic, the heart apparently only slightly if at all enlarged, the blood pressure 180 systolic and 130 diastolic. The twelve hours' urine contained 125,000 casts, all of the renal failure type, the number of red blood cells was 2,700,000 and of white blood cells and epithelial cells 109,000,000. There were 3094 mg. of protein per twelve hours with a volume of 773 c.c. and a specific gravity of 1.013. The blood urea concentration was 289 mg. per 100 c.c.

During the next three weeks the blood urea concentration fell to 89 mg. but thereafter again began to rise. Vomiting set in and the patient died of uremia two weeks later. There was no change in the character of the urine which was always dilute with 1,000,000 or 2,000,000 red blood cells per twelve hours. Casts, if found at all, were always renal failure casts.

PATHOLOGICAL OBSERVATIONS

Only the kidneys could be examined post mortem. They were reduced in size, averaging 8 × 6 × 3 cm. Their capsules stripped with some difficulty, leaving a granular reddish grey surface. The cut surface showed a definite reduction in the breadth of the cortex. The renal arteries were somewhat thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Only one or two glomeruli whose structure resembled their normal type can be found in a low power field. These glomeruli show varying degrees of fibrosis; the tuft is enlarged, and the capillaries are obliterated by the fibrous tissue and by a leucocytic infiltration with mononuclear and a few polymorphonuclear leucocytes. Bowman's space is obliterated by adhesions. By far the greater part of the glomeruli, 95 per cent of those counted in one section, show a complete transformation into hyaline connective tissue in which no capillaries but only a few atrophied fibroblasts and round cells persist.

Tubules. By far the greater part of the cortex is so filled with the proliferating fibrous tissue and leucocytic infiltration in the interstitial tissue that no convoluted tubules remain as such. Groups of atypical epithelium, or very tortuous channels lie surrounded by the inflammatory tissue. A few nests of more nearly normal tubules may be found usually lying just beneath the surface of the kidney. These are dilated and their lumens filled with granular or colloid material. In others are masses of polymorphonuclear leucocytes. In the collecting tubules are many large renal failure casts.

Interstitial Tissue. There is an extreme proliferation of the interstitial tissue throughout the cortex. The new tissue is densely fibrous, almost hyaline in places, but still contains many fibroblasts as well as large numbers of leucocytes. The latter are not only mononuclears but comprise a considerable number of polymorphonuclears.

Arteries. Many, but not all, of the arcuate arteries show a marked fibrous thickening of their intima and their adventitia is infiltrated with round cells. The smaller interlobular branches in the densely fibrosed cortex are greatly thickened.

SUMMARY

The kidneys show a very old but still active inflammatory process which involves the glomeruli and interstitial tissue. This has altered the whole normal relations of the cortical units, the tubules being greatly atrophied and destroyed. The arteries show a marked sclerosis.

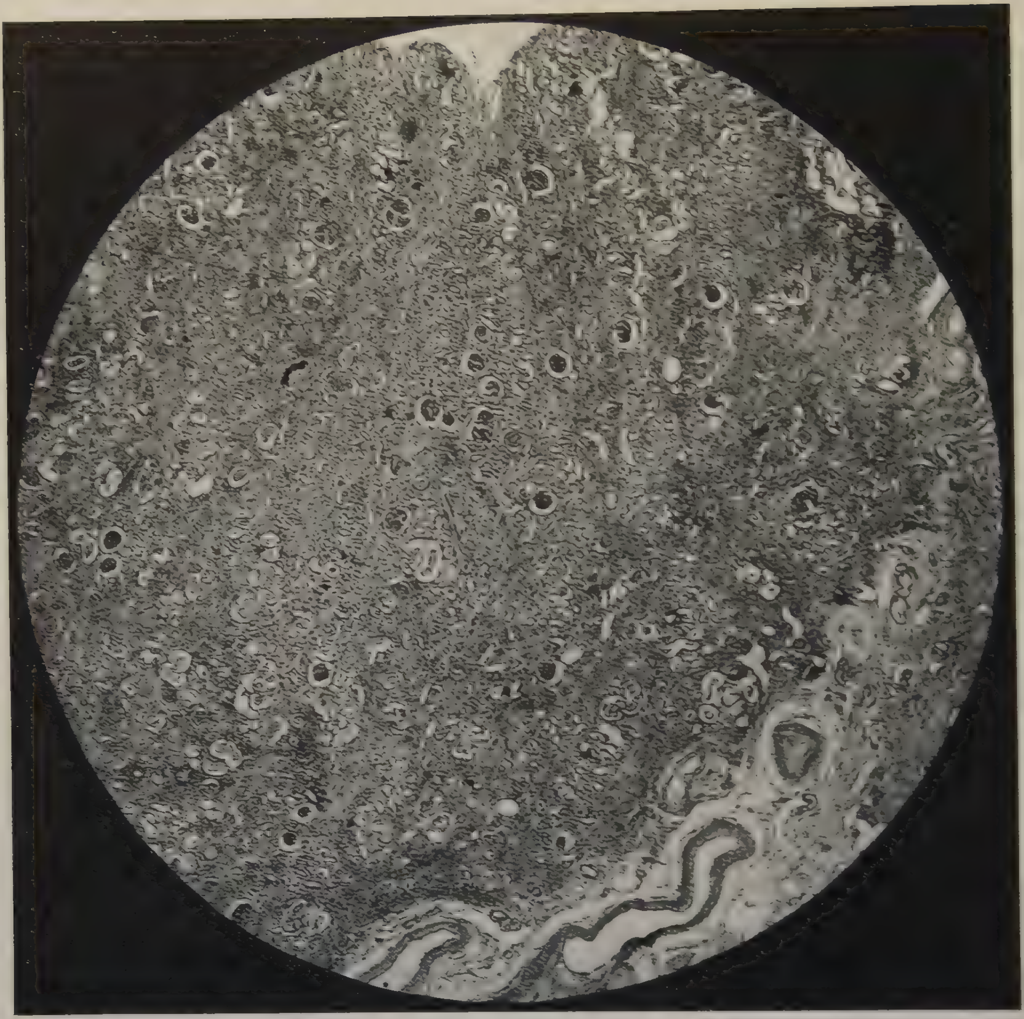

Plate XL a

The glomeruli though easily seen show varying stages of the inflammatory process. The interstitial tissue is irregularly proliferated with the usual resulting destruction and atrophy of the tubules or a converse dilatation of them. Some of the arteries are definitely sclerotic and deep scars may be seen on the surface.

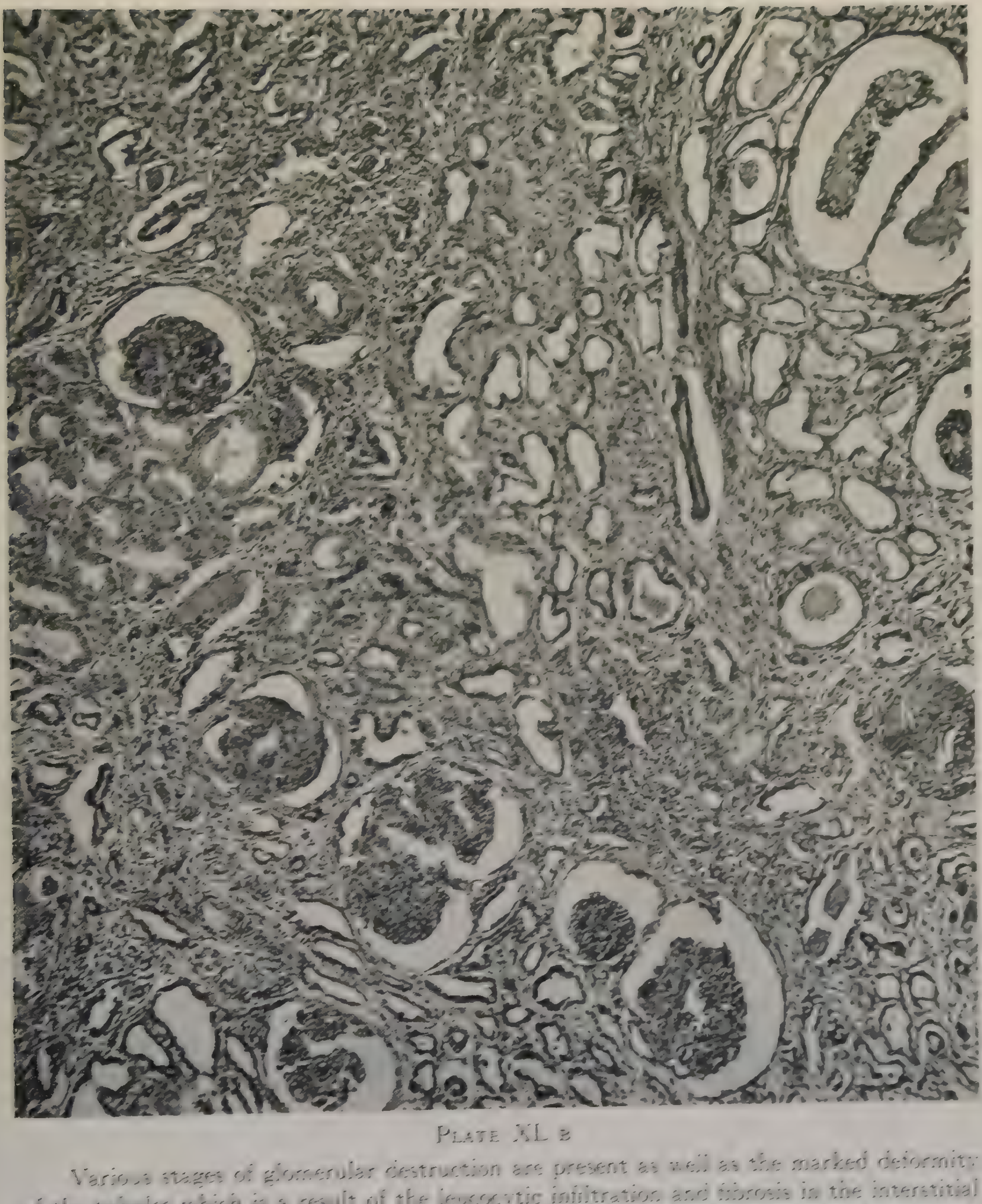

Plate XL b

Various stages of glomerular destruction are present as well as the marked deformity of the tubules which is a result of the leucocytic infiltration and fibrosis in the interstitial tissue. The tubules are filled with various types of casts. One glomerular tuft is greatly enlarged as a result of inflammatory reaction.

Case XLI

Bertha K. Aged forty-two.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. One year and eleven months. Observed during last four days.

Etiology. Uncertain.

Course. There was a clear history of an active inflammatory renal lesion in January 1920 followed by freedom from symptoms until November 1921, when uremia developed.

RELEVANT CLINICAL DETAILS

She has never been robust and she remembers that when she was a girl she was not able to run because she became short of breath. She was said to have been anemic at that time. Thereafter she remained free from any obvious illness until January 1920. A short time after a rather severe head cold a generalized edema developed. She noted that the urine was red in color and reduced in amount. As the edema cleared up in a few days she did not call in a doctor. She remained apparently in as good health as usual until November 2, 1921, when she was wakened at night by a sense of suffocation and had to sit up and gasp for breath. The persistence of these dyspneic attacks brought her to the hospital.

Physical examination disclosed a well-marked secondary anemia (red blood cells 2,900,000 per cubic millimeter), slight edema of the ankles and small amounts of fluid in both pleural cavities. The heart was greatly enlarged to the left, the blood pressure was 220 systolic and 120 diastolic. The retinal arteries were arteriosclerotic and here and there were patches of exudate.

A catheter specimen of urine contained so much albumin that it solidified on boiling. After centrifugalizing a thin layer of red blood cells could be seen above the white deposit of white blood cells, epithelial cells and casts. Large numbers of casts were seen. They were all of the renal failure type.

The patient relapsed into a stuporous state but with all the reflexes hyperactive. On November 14 clonic contractures of the muscles of the face, arms and legs were reported, which were more than tremors or twitches of the muscles but not sufficiently violent to be called convulsive. On that day the blood urea concentration was found to be 316 mg. per 100 c.c. Thereafter she fell into a deep coma in which she died on November 17, 1921.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a chronic tonsillitis, a secondary anemia and a healed apical tuberculosis and pleurisy. As a terminal infection an acute pericarditis was present. The kidneys were approximately normal in size, averaging 11 × 6 × 4 cm. The capsules stripped easily, leaving a fairly smooth congested surface in which an occasional petechial hemorrhage could be seen. The cut surface showed indistinct markings in the cortex. The renal arteries were essentially normal.

MICROSCOPICAL EXAMINATION

Glomeruli. The number of glomeruli is not greatly reduced, there being 8 to 10 fairly well preserved examples in every low powered field. None of them is normal, however, as in all there is a heavy leucocytic infiltration of the tuft with mononuclear and polymorphonuclear leucocytes. The capillaries are compressed and in many of them are fibrin thrombi. Some connective tissue proliferation can be found both in the tuft and as adhesions in Bowman's space, but the latter is in the great majority of cases still open, though it may contain leucocytes, fibrin and red blood cells. Very few completely fibrosed glomeruli are present.

Tubules. The convoluted tubules of the cortex still preserve their normal forms throughout the greater part of the section. Their epithelium shows a marked cloudy swelling, and in scattered tubules there is frank necrosis and desquamation of the cells. Other tubules are lined with a very atypical epithelium of the regenerated type. The lumen of every tubule is filled with either granular detritus or hyaline coagulated material. Red blood cells and polymorphonuclears are also found, as well as casts of all sorts including blood casts. In the collecting tubules of the medulla are large numbers of renal failure casts.

Interstitial Tissue. Throughout the cortex there is only a moderate increase in the interstitial tissue. There is some increase in fibroblasts and a moderate infiltration with mononuclear and polymorphonuclear leucocytes. In some places these processes are more extensive and cellular scars are found with some compression of the tubules.

Arteries. There is a moderate fibrous thickening of the intima of the arcuate arteries and some of the smaller interlobular branches are more prominent than usual on account of the thickening of their walls. There is quite a marked irregular congestion of the smaller vessels.

SUMMARY

The kidney shows a very active inflammation in the glomeruli and to a lesser extent in the interstitial tissue. Proliferative changes in the latter are only slight in degree. The tubules show active degenerative processes and there are many blood casts, and in the collecting tubules large renal failure casts. The arteries show some sclerosis.

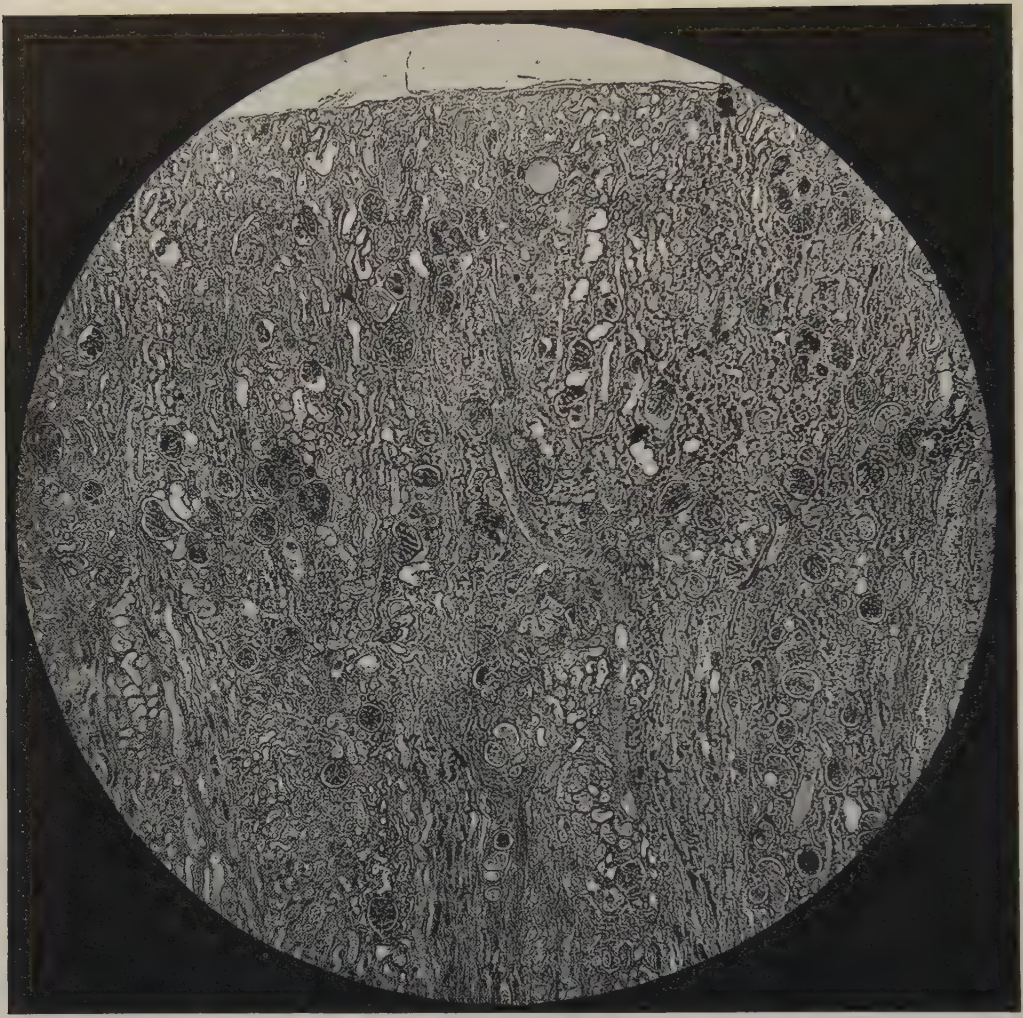

PLATE XLI A

The proliferation of the connective tissue is much less marked than is usually seen at this stage of hemorrhagic Bright's disease. As a result the tubules though filled with casts still preserve the normal arrangement to a fair degree. Many of the glomeruli are enlarged while others are contracted. It will be noticed that the surface of the kidney is smooth. No sclerotic vessels are present.

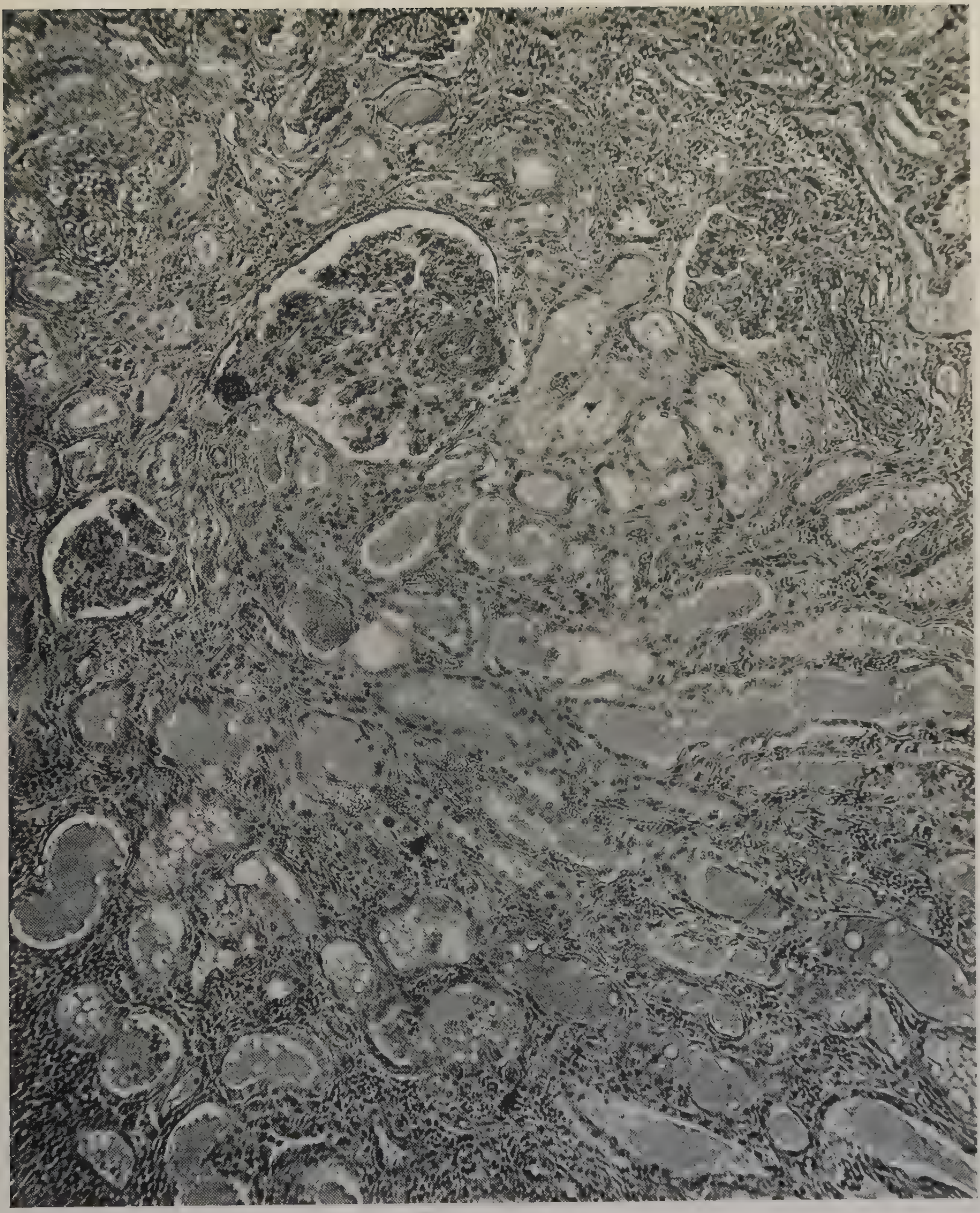

Plate XLI b

One glomerulus is enlarged by the inflammatory processes in its tuft. The tubules are filled with coagulated hyaline material. Throughout the interstitial tissue may be seen a heavy leucocytic infiltration.

CASE XLII

Leo N. Aged thirty-four.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown.

Etiology. No information.

Course. This patient happened to come under medical attention because he broke his arm. While under treatment in August 1925 he complained of dimness of vision and edema of the discs was found with evidences of old retinal hemorrhages. The heart was enlarged to the left, the blood pressure was 200 systolic and 140 diastolic. No history of any previous illness was obtained and the patient had not suffered from any symptoms which suggested vascular or renal disease. But in September he began to have headaches which were accompanied by nausea and later by vomiting. On the 20th of that month the blood urea concentration was found to be 270 mg. per 100 c.c. On October 14 a concentration test had a volume of 475 c.c. per twelve hours with a specific gravity of 1.014. There were 4,800,000 red blood cells and 9,000,000 white blood cells and epithelial cells in twelve hours' urine. The number of casts was 38,000 and all of them were renal failure casts. The rate of protein excretion was 2160 mg. per twelve hours. By October 18 the blood urea concentration was 332 mg. per 100 c.c. He was then obviously anemic and a count showed only 1,650,000 red blood cells per cubic millimeter. He passed into the coma in which he died on October 22.

PATHOLOGICAL OBSERVATIONS

Only the kidneys could be obtained after death. They were somewhat smaller than normal, averaging 10 × 5 × 3 cm. The capsules stripped with difficulty leaving a rough granular surface of greyish red color. The cut surface showed a reduction of the cortex. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are involved in the late stages of a chronic inflammatory process. In about one-sixth their number the tuft is still fairly well preserved, but shows a considerable development of connective tissue within it and a resulting collapse of the capillaries. There are also present many mononuclear and a lesser number of polymorphonuclear leucocytes and fibrin thrombi in the capillaries. Bowman's space is obliterated by fibrous adhesions or contains organized exudate and a few polymorphonuclears or definite capsular crescents. Other glomeruli show the development of more connective tissue and many, about half the total number, are reduced to hyaline masses of collagen.

Tubules. Throughout broad areas the convoluted tubules of the cortex are compressed by the proliferating connective tissue, so that they form irregular channels or solid clumps of atrophied cells. In other regions the tubules are hypertrophied and lined with a thick epithelium. This in many places shows parenchymatous degeneration and the lumens are filled with granular material. Others are dilated, lined with a flattened epithelium and filled with colloid-like material. Casts of all sorts, including blood casts, are present in the tubules, and in the medulla the collecting tubules contain large renal failure casts.

Interstitial Tissue. There is a marked irregular proliferation of the interstitial connective tissue throughout the cortex. This tissue is quite fibrous, but shows a diffuse infiltration with round cells and a few polymorphonuclear leucocytes. Where the scar tissue reaches the free surface deep retractions are formed.

Arteries. The arcuate arteries show a marked fibrous thickening of their intima and the smaller interlobular branches are also thickened but to a lesser degree.

SUMMARY

There is present in the kidney an old, but judging from the red blood cells and polymorphonuclear leucocytes, still active inflammatory involvement of the glomeruli and interstitial tissue. The tubules are either atrophied or hypertrophied. Active degenerative processes are present. The arteries show a moderate sclerosis.

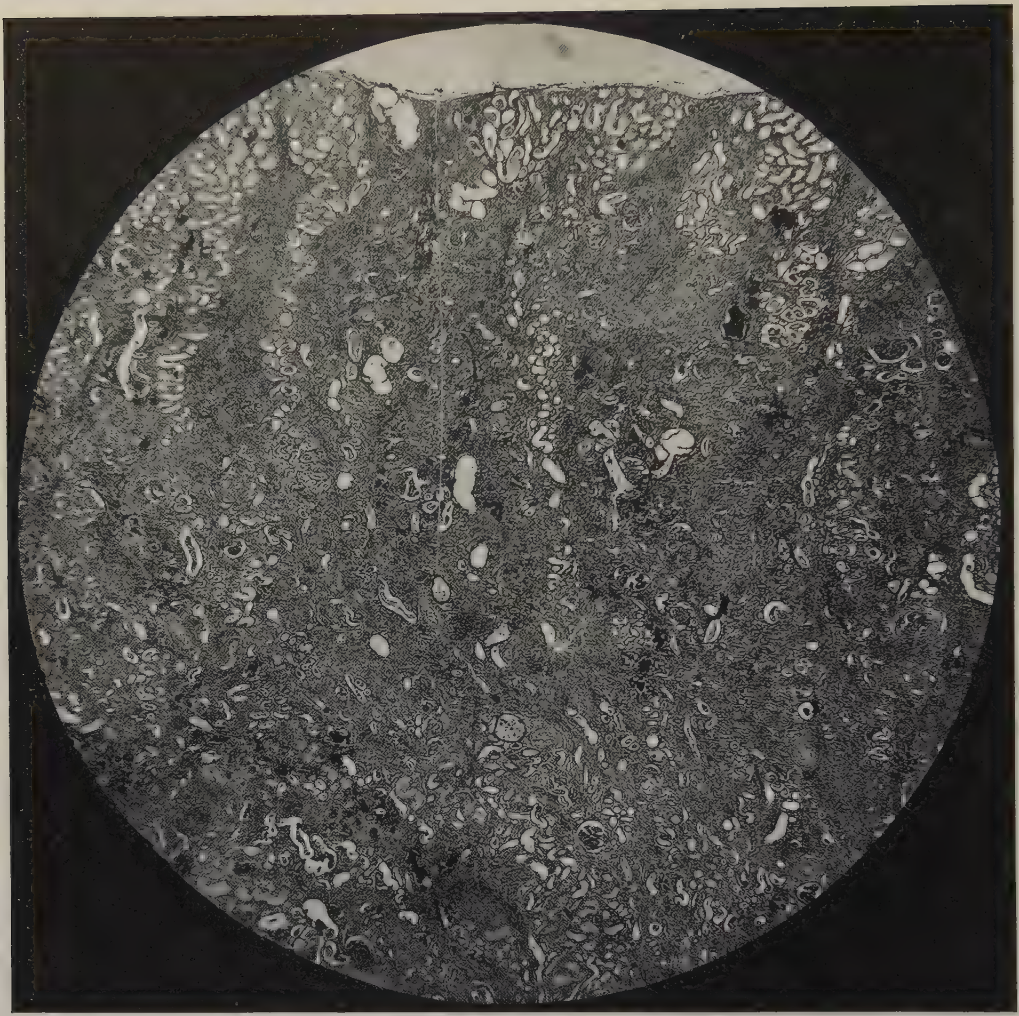

Plate XLII a

The glomerular tufts are almost entirely replaced by connective tissue and Bowman's space is obliterated by fibrous adhesions. The same inflammatory proliferation throughout the interstitial tissue has destroyed tubules through large areas whereas others remain of more or less normal size.

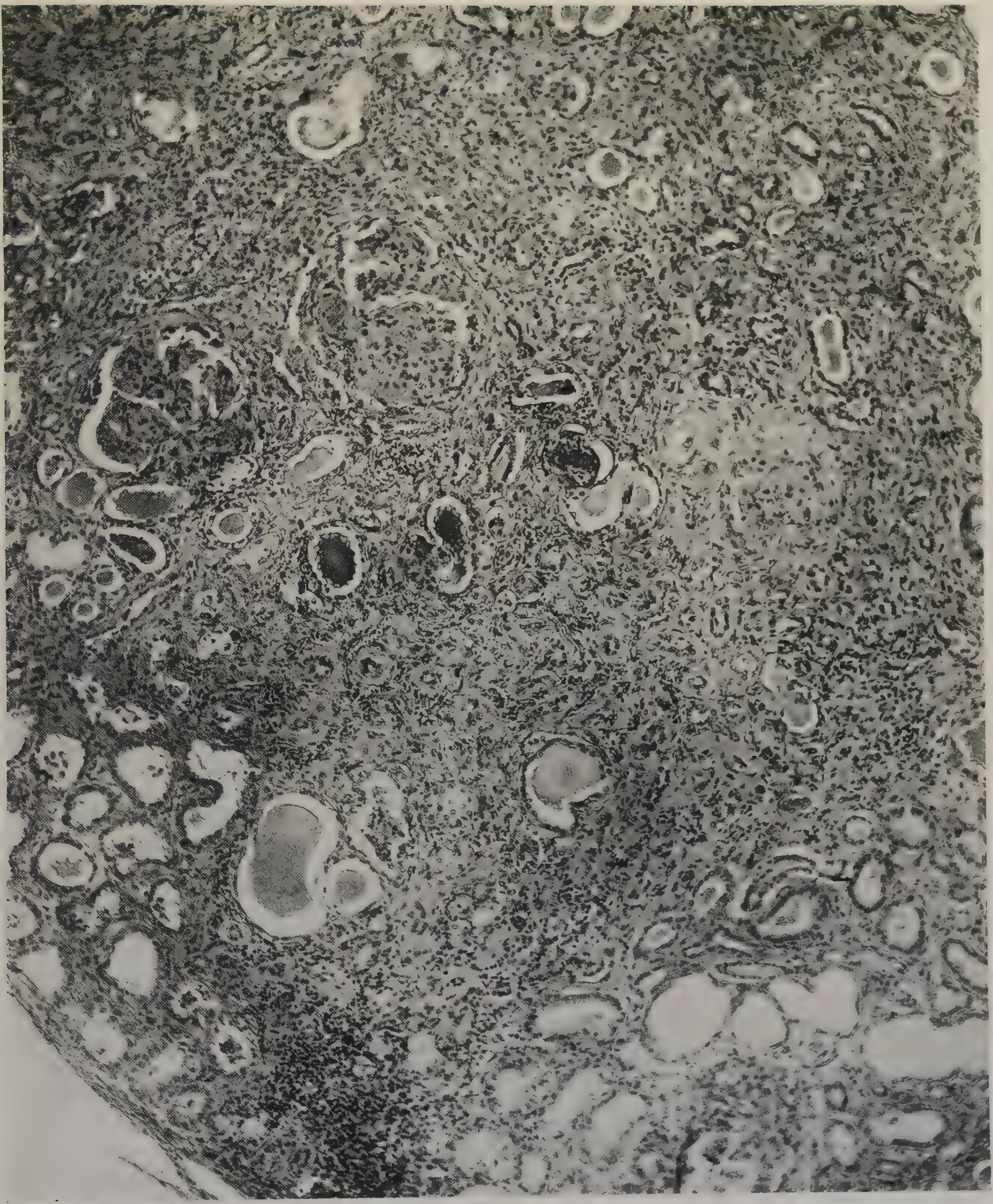

Plate XLII b

Only a very occasional glomerulus can be made out, the majority being blended with the connective tissue which so diffusely infiltrates the section. Tubular collapse alternates with dilatation.

CASE XLIII

Ralph S. Aged twenty-six.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Seven years. Observed during the last three and one-half years.

Etiology. Unknown.

Course. The initial stage occurred during the spring of 1917 but none of its symptoms were observed and the condition was discovered some months later in the latent stage. During the next four years the blood pressure was within normal limits and it was not until the autumn of 1921 that hypertension was noted. In January 1922 the sediment examination revealed an active stage of hemorrhagic nephritis and a reduction of the amount of functioning renal tissue to 41 per cent of the normal. In September 1923 the renal tissue was reduced to 13 per cent of the normal and renal failure casts indicated the onset of the terminal stage. He died of uremia in July 1924.

RELEVANT CLINICAL DETAILS

The exact time of onset is uncertain. He had had repeated tonsillitis but in the spring of 1917 the urine was reported as normal when he enlisted in the National Guard and again when it was examined three months later at Camp Kearny. But in the autumn of the same year he was admitted to the hospital on account of an accidental injury and a routine examination revealed the presence of albumin, blood and pus cells in the urine. After ureteral catherization he was told that the condition was bilateral and was not tuberculosis. A diagnosis of acute nephritis was made which was changed to chronic nephritis after a month's observation. He was discharged from the service.

His health was fairly good until April 1921 when he had high fever for a week. In May 1921 he had tonsillitis with a temperature of 103°F. Throughout this period of four years his systolic blood pressure was always less than 130, but some albumin was constantly in the urine. In October 1921 he began to suffer from headaches and the systolic pressure was 165. The headaches continued to recur but at the next examination the systolic pressure was 140. About this time he began to suffer from dyspnea on exertion and from precordial pain and in December 1921 he had fever and severe pain in his chest which was diagnosed as due to pleurisy. During this month the systolic pressure varied between 140 and 195.

In January 1922 when he was first seen the heart did not seem to be enlarged. The blood pressure was 130 systolic and 90 diastolic. The palpable arteries were not noticeably thickened. The red blood cells were 4,200,000 per cubic millimeter and the hemoglobin 83 per cent. The concentration test gave a volume of 508 c.c. per twelve hours with a specific gravity of 1.026. The rate of protein excretion was 5870 mg. per twelve hours. The most striking feature of the sediment was the large number of fat droplets. Of the casts 49 per cent were entirely covered with fat droplets and were classified as fatty casts. Many of the fat droplets were doubly refractile. There were many oval cells full of fat droplets. They were about twice as large as white blood cells and when the fat was dissolved by ether were seen to contain a small oval nucleus. There were 5 per cent epithelial, 23 per cent granular and 23 per cent hyaline casts. After abstention from fluids and administration of urea the maximum concentration of urea in the urine was 2.13 per cent. The urea ratio test showed that 41 per cent of the normal amount of renal tissue was still functioning.

A year later renal failure casts were found and the quantity of renal tissue was estimated as only 13 per cent. Yet in September 1923 his general condition had improved and the headaches though they still recurred were less severe. In March 1923 he had had a period of fever on account of an infection of the jaw subsequent to a tooth extraction. In August 1923 he suffered from a middle ear infection which drained spontaneously. A pure culture of a streptococcus was obtained. Shortly afterwards both the antral sinuses were opened and found to contain pus. Blood pressure readings had been made every month since January 1922. The systolic had never been less than 150 and the average was about 170. On examination in September 1923 the systolic pressure was 170 and the diastolic 100. The concentration test gave a volume of 645 c.c. per twelve hours, with a specific gravity of 1.013. The rate of protein excretion was 3510 mg. per twelve hours. There were 655,000 casts in twelve hours, 139,000,000 red blood cells and 30,000,000 white blood cells and epithelial cells. There were no longer any fatty casts, but the percentage of renal failure casts had increased from 13 per cent to 58 per cent. The blood urea concentration was 125 mg. per 100 c.c.

In March 1924 he again returned to San Francisco for examination. In the interim he had grown much weaker and the headaches were at times extremely severe and accompanied by vomiting. He was very pale. The hemoglobin percentage was only 35 per cent. During the last four months his temperature had risen to 99° or 100°F. every evening; the systolic pressure had never fallen below 200, and had averaged 220 systolic and 120 diastolic. After a few days in bed, however, the systolic pressure fell to 150, though the diastolic was still 120. There was evidence now of definite cardiac enlargement. The volume of the twelve hours' urine was 708 c.c. with a specific gravity of 1.014. The rate of protein excretion was 2810 mg. per twelve hours. The number of casts per twelve hour period was 116,000. All of them were renal failure casts. The red blood cells numbered 50,000,000 per twelve hours and the white blood and epithelial cells 4,500,000. On March 7, 15 and 26, blood urea concentrations of 206, 214 and 283 mg. per 100 c.c. were found, but he nevertheless felt stronger and was free from headache. The blood pressure which had previously been so high never exceeded 155 systolic and 120 diastolic and at times was as low as 140 and 90, although there was no evidence of cardiac failure.

In June 1924 he again came back. In May he had grown very weak and at another hospital it was found that his hemoglobin had fallen to 23 per cent with 1,420,000 red blood cells per cubic millimeter. He had been given three blood

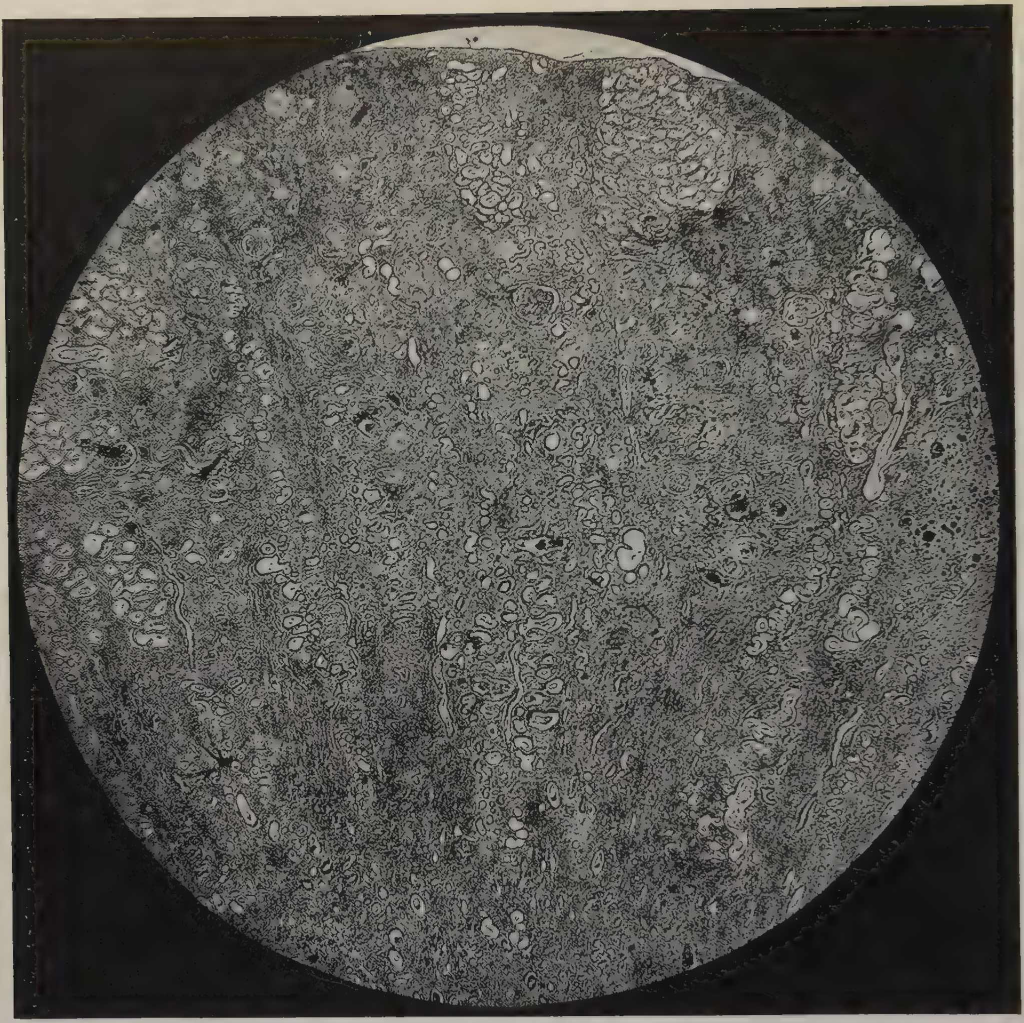

Plate XLIII a

There is a very diffuse fibrous proliferation of the connective tissue framework of the kidney in which are scattered irregular areas of cellular infiltration. An occasional glomerulus can be seen lying in the sclerotic tissue along with areas of hypertrophied tubules.

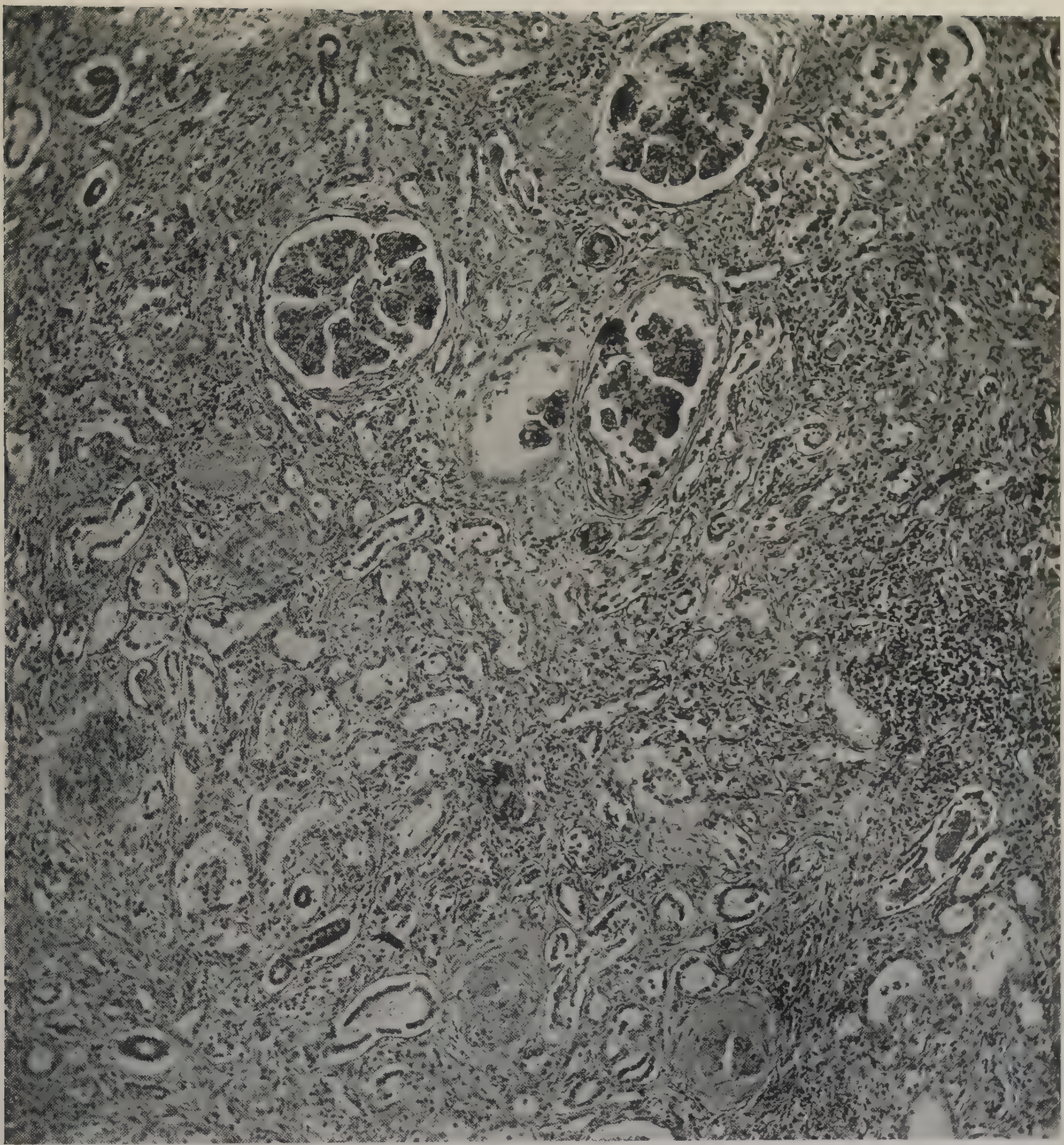

Plate XLIII b

There is a marked leucocytic infiltration and fibrous tissue proliferation throughout the interstitial tissue with the usual destructive effects on the tubules. The glomeruli are in different stages of the inflammatory process. Note the two hyaline remains of tufts at the extreme bottom of the plate. (Cf. Plate xcvi.)

transfusions which raised his hemoglobin to 35 per cent and the red blood cells to 2,800,000 per cubic millimeter. The blood urea concentration had been 293 mg. per 100 c.c. but had decreased for a time to 212 mg. after the administration of much water. In June when he came in while passing through San Francisco it was 259 mg. per 100 c.c., and the casts were again found to be all of the renal failure type. He died a month later. The results are given in Table XXXIV.

TABLE XXXIV

Date	Number of casts in 12 hrs.	Differential							R.B.C. 12 hrs.	W. & Ep. 12 hrs.	Protein mg. 12 hrs.	Vol. sp. gr.	Blood urea	Renal tissue per cent of normal
		BL. per cent	EP. per cent	GR. per cent	FA. per cent	W. per cent	HY. per cent	Renal fail. per cent						
1922 Jan........	11,700	0	5	23	49	0	23	0	....	....	5,870	508 1.026	38	41
1923 Jan........	7,900,000	0	6	1	8	6	66	13	....	....	4,320	600 1.020	...	13
Sept.......	655,000	0	3	3	..	..	36	58	139,000,000	30,000,000	3,510	645 1.013	125	
1924 March......	116,000	0	0	0	0	0	0	100	50,000,000	4,500,000	2,810	710 1.014	206	
June.......	....	..	..	..	..	..	..	100	....	....	......	.....	259	
July........	Died													

PATHOLOGICAL OBSERVATIONS

The kidneys only were obtained at autopsy. They were of equal size, measuring 9 × 3 × 2 cm. The capsule stripped easily, leaving a rather pale finely granular surface. The cut surface showed a definite reduction of the cortex; the medulla and pelvis were normal. The renal arteries were not thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all of the glomeruli are involved in the later stages of glomerulitis. There is a development of connective tissue within the tuft varying from a just perceptible thickening of the intracapillary tissues to the production of large masses of collagen which compress the tuft and obliterate the capillaries. Many are completely fibrosed by this process. Around the tuft there is also involvement of the capsular spaces, such as the production of glomerular crescents, adhesions and development of definite fibrous connective tissue adhesions. Both in the tuft and in the capsular thickenings are a moderate number of leucocytes. These are chiefly round cells with a few polymorphonuclear leucocytes.

Tubules. The convoluted tubules of the cortex are very irregular in size and shape. In the areas of interstitial fibrosis they are greatly compressed and atrophied, many existing only as solid cords of cuboidal cells. In those few areas which are comparatively free of fibrosis the tubules are larger than normal and are lined with a thick epithelium. The epithelial cells show only slight degrees of parenchymatous degeneration. Practically all the tubules contain either granular material or organized casts. The latter are of all types, epithelial, granular and hyaline. Occasionally collections of red blood cells are seen. In those convoluted tubules which are dilated, the epithelium is compressed to a low cuboidal layer and the cyst-like lumen is filled was a mass of hyaline colloid material. The ascending limbs of Henle's loop contain casts similar to those described. Practically all of the terminal ducts of Bellini are filled with large broad renal failure casts. All stages of their formation, from the accumulation of masses of granular detritus to the consolidation of this material into definite well-formed plugs can be observed. (Fig. 17.)

Interstitial Tissue. There is a marked proliferation of the connective tissue throughout the cortex with a resulting compression and atrophy of the tubules as described previously. Throughout this connective tissue there is a heavy leucocytic infiltration, the majority of the cells being lymphocytes with a moderate number of polymorphonuclears. There is a definite proliferation of connective tissue in the medulla, but to a lesser degree.

Arteries. There is a moderate fibrous thickening of the intima of the larger arteries, and about some, perivascular fibrous thickening and round cell infiltration.

SUMMARY

The kidneys show a late intracapillary and extracapillary glomerulitis, with interstitial fibrosis and destruction of the cortex. There is a moderate sclerosis of the arteries.

Case xliv

William V. Aged thirty-five?

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Unknown. Observed for one month.

Etiology. No information.

Course. In 1918 a gunshot wound of the hand was followed by cellulitis. This was the only illness he can remember. In August 1925 his ankles and face became swollen and two weeks later he had a transient blurring of vision. On the twenty-first of that month physical examination disclosed anemia (red blood cells 2,560,000 per cubic millimeter), generalized edema, marked cardiac enlargement, and a blood pressure of 200 systolic and 105 diastolic. On September 10, 1925 the twelve hours' urine contained 239,000 casts which were all renal failure casts. The number of red blood cells was 12,000,000 and there were 11,000,000 white blood cells and epithelial cells per twelve hour period. The rate of protein excretion was 1520 mg. per twelve hours. Fluid had collected in the pleural cavities and the concentration of urea in a sample of this fluid was 465 mg. per 100 c.c.

The patient had been vomiting for some time. On September 10 he was almost comatose. He died on September 18.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained after death. They were reduced in size, averaging 9 × 5 × 3 cm. Their capsules stripped with some difficulty, leaving a granular reddish purple surface. The cut surface showed a fibrosis and reduction in the breadth of the cortex. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. About 3 or 4 glomeruli whose general structure is still fairly well preserved can be found in each low power field. Their tufts are swollen, and show an infiltration with mononuclear and polymorphonuclear leucocytes. Fibrin thrombi are present in some of the capillaries and there is a varying amount of fibrosis with consequent collapse of the capillaries. Bowman's space contains granular material and is more or less obliterated by fibrous capsular adhesions. Other glomeruli, about two-thirds the total number, are reduced by the chronic proliferative process in them to masses of hyaline connective tissue.

Tubules. There is a very irregular scarring of the cortex which has reduced the convoluted tubules to atrophic cords and channels. About two-thirds the area of the cortex is thus occupied. In the remaining portions the tubules are much larger than normal. Most of them show a true hypertrophy, the lining epithelium being greatly increased in thickness. These cells show in many places a marked cloudy swelling of the more severe type, and their lumens are filled with granular material. In others the epithelium is compressed and atrophied by the colloid-like material that fills them. The straight tubules of the deeper layers of the cortex contain casts of all sorts, including blood casts and in the collecting tubules are many large renal failure casts.

Interstitial Tissue. The greater part of the cortex is occupied by dense fibrous tissue in which are areas of heavy leucocytic infiltration. Most of these cells are mononuclears, though a few polymorphonuclears may be found among them. Where this tissue reaches the free surface of the kidney retracted scars are formed, between which lie the groups of hypertrophied tubules previously described.

Arteries. There is a very marked fibrous thickening of the intima of the larger arteries and the smaller interlobular branches to the cortex show a diffuse thickening of their walls.

SUMMARY

The kidneys show a late stage of chronic inflammatory processes involving the interstitial tissue and the glomeruli. The presence of red blood cells and polymorphonuclear leucocytes is evidence that the lesion is still active. The tubules are either compressed or hypertrophied and present active degenerative changes. The arteries show a marked sclerosis.

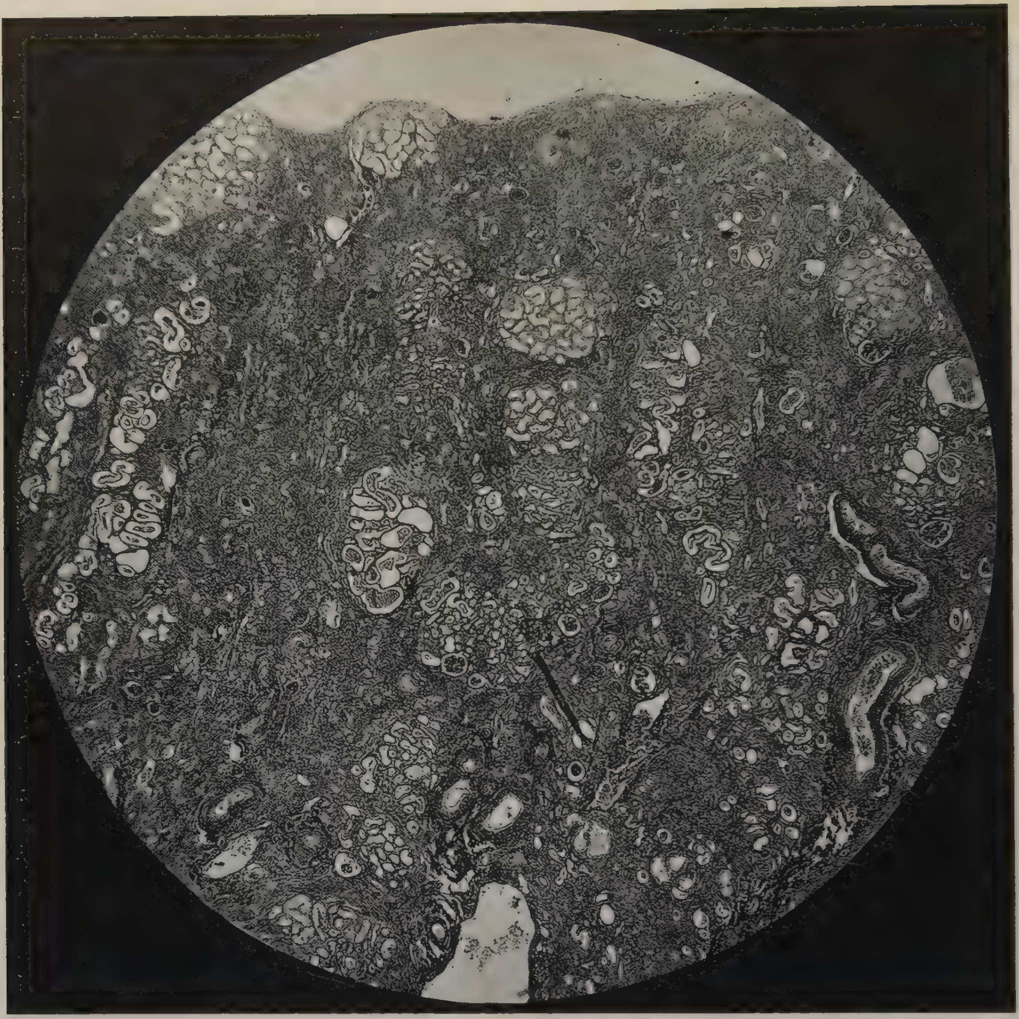

Plate XLIV a

There is a very marked irregular proliferation of the connective tissue and heavy round cell infiltration of it. In this fibrous tissue lie islands of tubules which are either hypertrophied or dilated and filled with debris. A large dilated vein is seen at the lower part of the section and there are many sclerotic arteries. The surface of the kidney is extremely irregular.

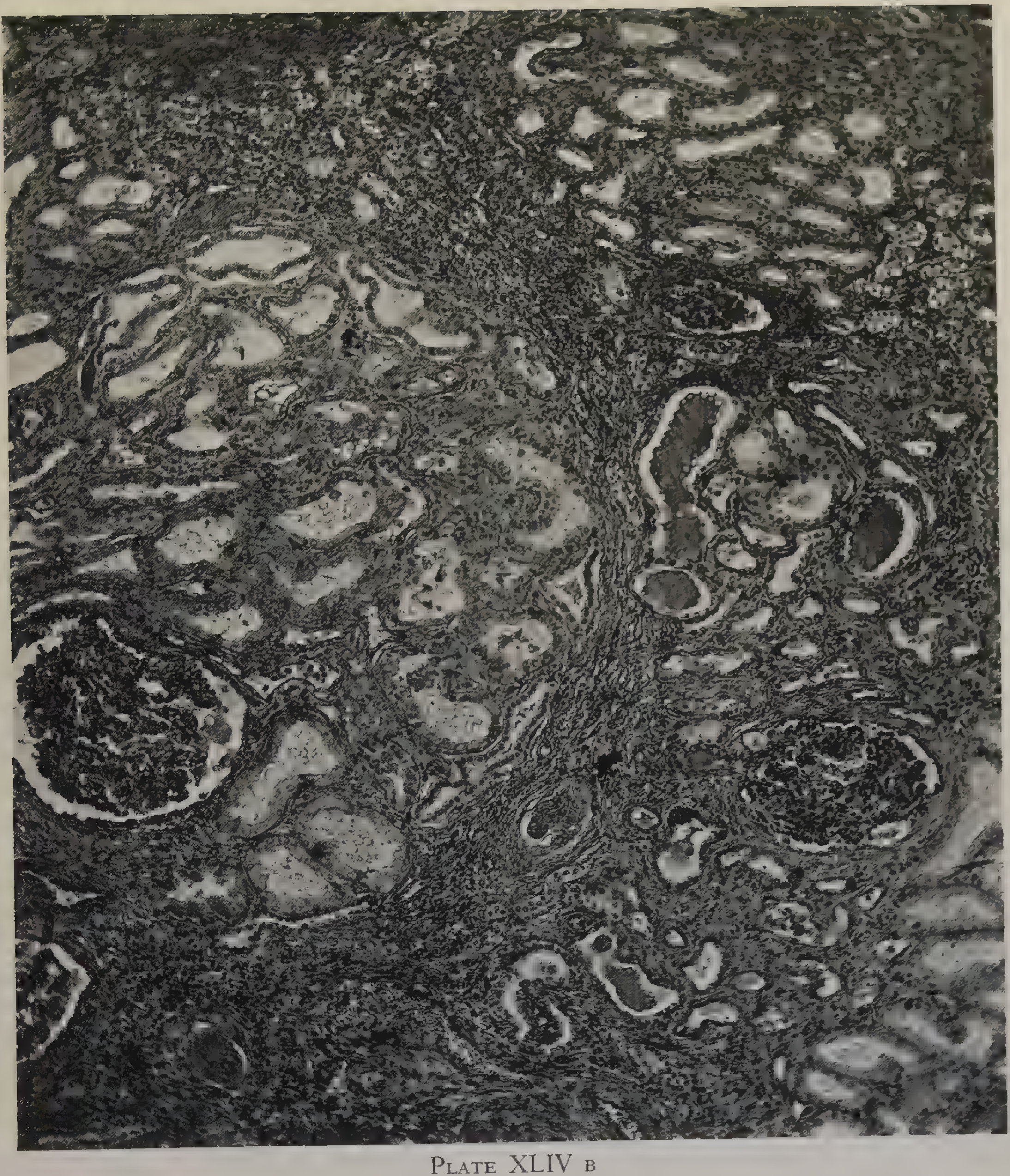

Plate XLIV b

The irregular connective tissue proliferation in the interstitial tissue has left islands of tubules in which is seen a compensatory hypertrophy. The glomeruli are densely infiltrated with leucocytes. (Cf. Plate xcvii.)

CASE XLV

John W. Aged forty-two.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Etiology. Unknown.

Duration. Five years or more. Observed during the last one and one-half months.

Course. In 1915 he noticed dyspnea on exertion and occasional dizziness but he was in fair health until February 1920 when these symptoms became more marked and were accompanied by a rapid loss in weight. In May 1920 he had hemiplegia and during his convalescence the vision in his right eye became blurred. When he came under observation in July 1920 an active exudative retinitis and marked hypertension were found. He died in uremia in August 1920.

RELEVANT CLINICAL DETAILS

There was nothing in the past history of the patient which suggested the onset of a hemorrhagic Bright's disease, nor was there even any knowledge that he had a renal lesion of any sort. But he stated that for some years, at least five, he had been obliged to get up two or three times every night to pass urine. It was five years before that he had first noticed that he was short of breath when climbing stairs and thereafter he had been troubled with dizziness. He did not think there was anything seriously wrong until seven months before his death when the dyspnea became more marked. His weight fell from 220 lbs. to 174 lbs. in the course of two months. Three months later he woke one night to find that his entire right side was paralyzed. Two weeks later when he was beginning to be able to move his limbs, he found that he could not see clearly with his right eye.

When he was first seen one and one-half months before his death he was found to have a greatly enlarged heart, but there was no cyanosis or edema. The red blood cells numbered 3,500,000 per cubic millimeter. The systolic pressure was 235 and the diastolic 150. The arteries were throbbing but were not markedly thickened or tortuous. There was an extensive neuroretinitis with fresh exudate. The blood urea concentration was 72 mg. per 100 c.c. Successive determinations showed a steadily progressive increase until the level of 350 mg. per 100 c.c. was reached on the day before his death.

At the early date (1920) at which this patient was seen the urinary observations leave much to be desired. The urine was of low specific gravity and clear. In one twelve hours' urine 2880 mg. of protein were found. The sediment contained an abnormal number of red blood cells and a large number of granular and waxy casts. The drawings show that many of these were unusually broad. Although the evidence is not conclusive it seems likely that this patient had reached the terminal stage of a long unsuspected hemorrhagic Bright's disease.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a general arteriosclerosis with marked involvement of the abdominal aorta, coronary and cerebral vessels. The heart was twice its normal size, its enlargement being due to both a hypertrophy and dilatation. In the pons was an old apoplectic cyst. There was some edema of the legs and a small collection of fluid in the serous cavities.

The left kidney measured 12 × 5.5 × 7.5 cm. Its capsule was thickened and somewhat adherent and when removed left a distinctly granular surface of brownish color. On the cut surface the cortex was thin. The renal arteries were greatly thickened. The right kidney was the same as the left.

MICROSCOPICAL EXAMINATION

Glomeruli. Scattered throughout the cortex are many glomeruli which are practically normal. Some have a normal structure but are enlarged. In others, approximately one-half, there are various stages of obliteration by fibrous connective tissue, ranging from a peripheral deposit of collagen in the tuft to complete hyalinization of it. In none is any definite inflammatory exudate or hemorrhage found.

Tubules. The convoluted tubules of the cortex are very uneven in size, due to the presence of the fibrosis of the interstitial tissue. In some areas they are of normal size and their epithelium, save for a slight cloudy swelling, is normal. In the regions of fibrosis the tubules have atrophied to almost complete disappearance, and consist of small solid cords of epithelium. In still other regions there is a marked hypertrophy of the tubules and they are lined with large cuboidal cells many times the size of the normal units. Some of these large cells are filled with colloid droplets. The straight tubules of medulla are essentially normal, though there are many casts present in them, principally of the hyaline type. The dilated convoluted tubules also contain casts, mostly very large ones composed of colloid.

Interstitial Tissue. There is a very marked proliferation of the interstitial tissue, particularly in the cortex, but also in the medulla. The proliferation is mostly of fibrous connective tissue with the development of dense collagen arranged in scattered focal scars, accompanied by a moderate round cell infiltration with mononuclears. Between these scars lie the groups of hypertrophied tubules previously described.

Arteries. The arteries throughout the entire kidney show a very marked sclerosis, which consists of an extreme fibrous thickening of their intima. Even the small vessels in the outer parts of the cortex show the lesion to a marked degree.

SUMMARY

The kidneys show a marked arteriosclerosis of the renal vessels, an accompaniment of a general involvement of the arteries. There is extensive scarring of the cortex with atrophy of the tubules and epithelium and hyalinization of the glomeruli. No exudative inflammatory lesions are present.

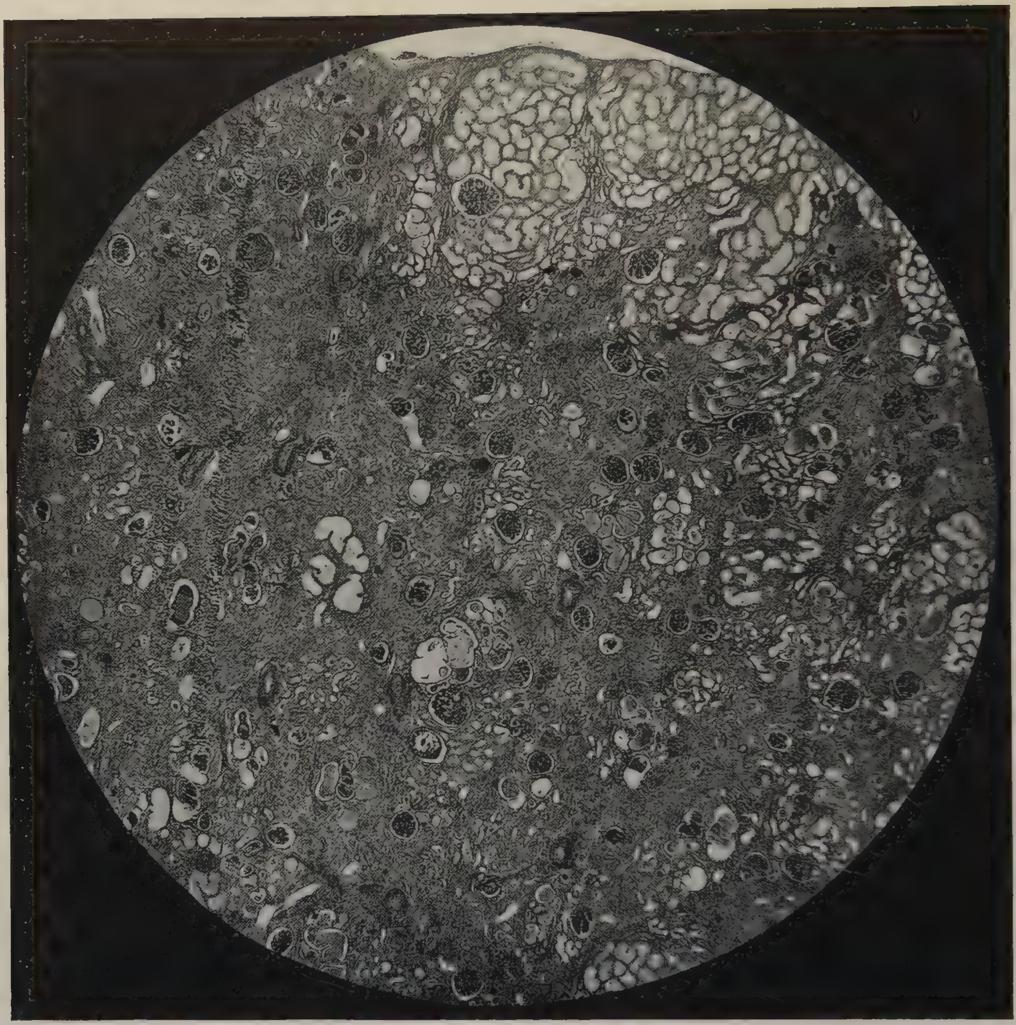

Plate XLV a

There is an extreme irregular inflammatory proliferation of connective tissue which destroys the architecture of the cortex. In the scar tissue many small thickened arteries may be seen, tubules are collapsed and glomeruli sclerosed. Near the surface are some nests containing hypertrophied glomeruli and tubules and similarly affected structures are seen scattered all through the section. The granulations of the surface of the kidney show quite plainly.

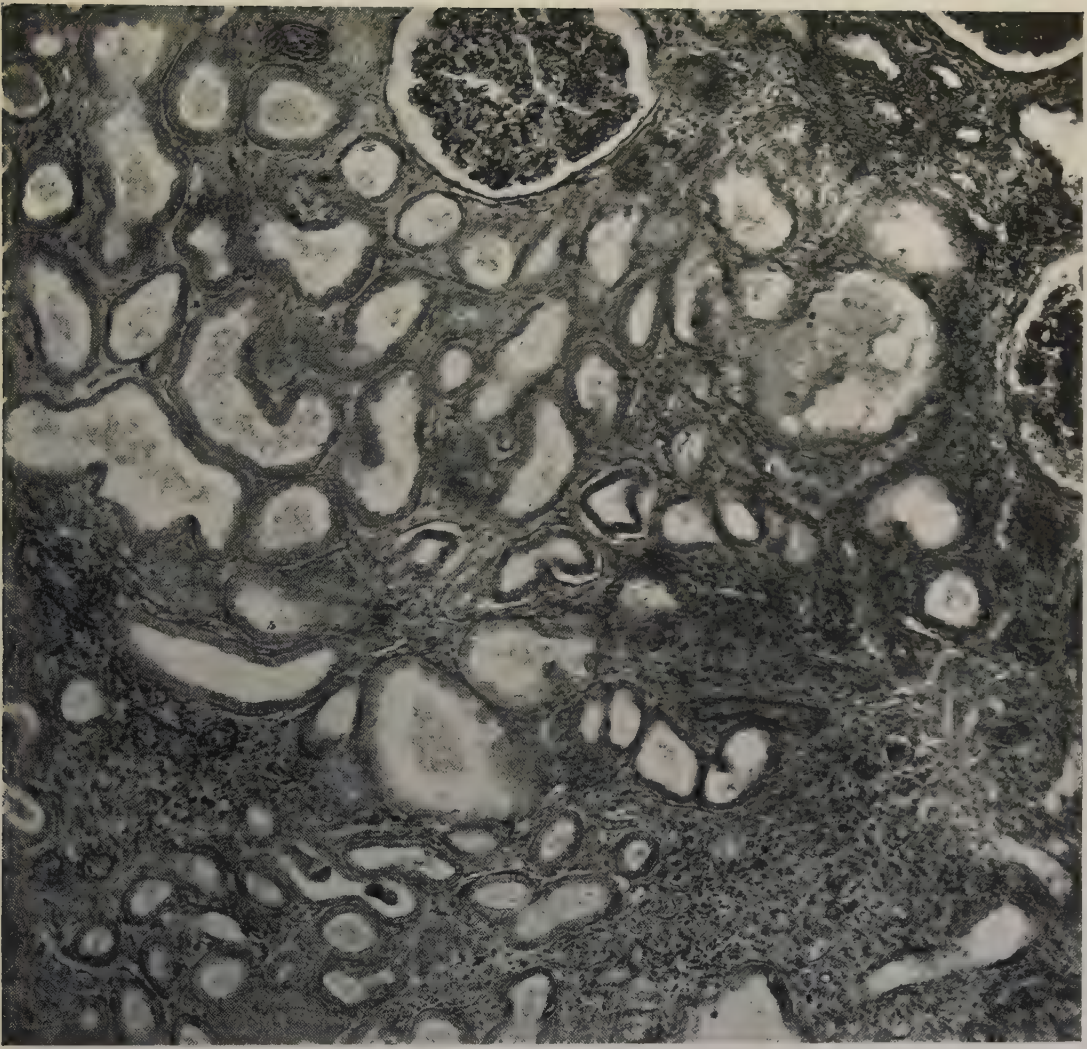

Plate XLV b

A group of hypertrophied convoluted tubules is seen. In the remainder of the field the scar tissue has compressed and distorted these structures. The glomerular tufts in the plate are fairly well preserved.

Case xlvi

William Z. Aged fifty-five.

Clinical Diagnosis. Hemorrhagic Bright's disease, terminal stage.

Duration. Probably fifty years. Observed during the last seven and one-half years.

Etiology. Unknown.

Course. In 1880 when five years old, while recovering from whooping cough, he developed a generalized edema. Albumin was found in his urine. Up to 1885 the albuminuria was constantly found and at times he was edematous. Thereafter his health improved and albuminuria was not noted again until 1919 when a routine examination showed its presence. When seen in 1923 he was in the latent stage. There was a slow downward progression during the next seven years until his death in uremia. The symptoms were predominantly vascular and the renal lesion showed very little activity.

RELEVANT CLINICAL DETAILS

Fifty years before his death, when he was five years old, he was quite ill after whooping cough. He was later told that this was the first time he had a generalized edema and that the doctor examined the urine and finding albumin diagnosed an acute nephritis. He himself remembers that up to the age of ten years he had recurrent edema and that his urine constantly contained albumin. Thereafter however his health markedly improved and he never afterwards was edematous. He thought that the albuminuria also had gone.

During the next twenty-nine years (1890 to 1919) his health was good except for one period of four years during which he suffered a good deal from an antrum infection. After an operation in 1915 he was relieved of this also.

In 1919 he began to have occasional headaches and it was in this year that a routine examination of the urine made at the time of his discharge from the army disclosed the presence of albumin in his urine. He was sent to an army hospital and was under treatment for seven weeks. A tonsillectomy was performed.

In 1920 his occasional headaches became more frequent and much more severe, and when he was first seen in April 1923 they recurred nearly every week and were very disabling. There were obvious indications of arteriosclerosis, though his heart was not noticably enlarged. His blood pressure was 160 systolic and 110 diastolic.

At that time (seven and one-half years before his death) it was found that only 32 per cent of the average normal amount of renal tissue was still left. But in this case the low level was for a long time remarkably well maintained, and uremia was warded off for more than seven years.

The long continuance of this preuremic state may be connected with the low level of activity of the renal lesion. The data are given in Table xxxv. In spite of the fact that there was reason to believe that the lesion had existed for forty-five

TABLE XXXV

Date	Number of casts in 12 hrs.	Differential (per cent)							R.B.C. 12 hrs.	W. & Ep. 12 hrs.	Prot. mgm. 12 hr.	Vol. sp. gr.	Blood urea	Renal tissue per cent of normal	Bl. press.		Clinical notes
		BL.	EP.	GR.	FA.	W.	HY.	Broad							Sy.	Dia.	
1923, April	135,000	31	7	8	1	6	25	21	1,600,000	900,000	150	684 / 1.018	...	32	160	110	
1923, Sept.	19,000	+	4	4	0	4	88	+	7,000,000	420,000	130	672 / 1.019	...	36	165	120	Climbing in Sierras for a month. Felt very well.
1923, Nov.	47,000	38	0	9	0	3	34	16	3,500,000	310,000	98	330 / 1.030	...	31			
1924, March	36,000	33	0	0	0	0	67	0	16,300,000	950,000	100	510 / 1.017	...	32	170	125	Left hemiplegia. Recovery in six months.
1925, Sept.	12,000	29	0	0	0	0	71	0	1,600,000	280,000	52	370 / 1.018	...	..	150	105	No headaches since hemiplegia. Feels well.
1925, Feb.	22,000	15	0	0	0	0	67	0	16,000,000	750,000	......	414 / 1.021	61	..	110	90	Recovering from "influenza."
1925, March	15,000	4	0	0	0	0	92	4	6,000,000	400,000	60	308 / 1.021	...	26	130	95	
1926, May	12,000	6	0	6	0	0	54	34	23,000,000	680,000	140	520 / 1.016	43	30	180	95	
1926, Nov.	13,000	..	..	..	..	..	..	..	13,000,000	450,000	......	.....	54	..	160	120	
1927, Jan.	12,000	..	..	..	..	..	..	...	15,000,000	....	191	414 / 1.018	...	..	170	125	Another attack of "influenza."
1927, June	39,000	..	..	..	..	..	..	...	20,000,000	380,000	203	381 / 1.016	...	26	140	110	
1928, Jan.	37,000	..	..	..	..	..	..	...	17,000,000	378,000	223	378 / 1.018	...	..	160	140	
1928, July	6,000	..	..	..	..	..	..	...	20,000,000	680,000	416	578 / 1.014					
1929, July	....	..	..	..	..	..	..	...	....	....	......	.....	99	..	180	115	Just back from a month of climbing in high Sierras.
1929, Sept.	0	..	..	..	..	..	..	...	15,000,000	....	464	560 / 1.015	85	..	165	100	Gout. Anemic.
1930, June	18,000	..	..	..	..	..	..	100	49,000,000	1,750,000	1,592	790 / 1.014	151	..	250	140	Complains of muscle cramps. Small retinal haemorrhage.
1930, Aug.	0	..	..	..	..	..	..	...	9,000,000	800,000	1,357	880 / 1.010	140	..	180	120	Cramps annoy him but still working steadily.
1930, Oct.	....	..	..	..	..	..	..	...	....	....	......	.....	...	..	...	...	Died in uremia, coma.

years it will be noted that for three years the sediment findings are typical of the latent stage: a rate of red blood cell excretion in the millions or tens of millions, no evidence of any appreciable degenerative lesion, only small quantities of protein, and small numbers of casts among which were included a considerable proportion of blood casts.

In 1924 he was disabled by hemiplegia but within six months there was an almost complete functional recovery. The extremely severe headaches from which he had suffered since 1920 never thereafter returned and he went back to his work of preaching and of administration with renewed vigor.

In the autumn of 1929 he had typical gout in one foot and until the end was liable to occasional severe attacks. They appeared to be greatly shortened by the intravenous injection of 25 per cent glucose solution.

In the summer of 1929 he began to pass into the terminal stage. He was now somewhat anemic and in July when he returned from a month's holiday in the high Sierras his blood urea concentration had risen to 99 mg. per 100 c.c. In 1927 the amount of renal tissue as measured by the urea ratio was only 26 per cent of the normal average and at that time the sediment counts had indicated that the lesion in this remnant of kidney was relatively inactive, for the casts had not exceeded 50,000 nor the protein excretion been over 200 mg. since 1923. But in 1929, when presumably a still smaller fraction of the usual number of renal elements remained, the dilute urine it secreted contained more than twice as much protein and by June 1930 when the blood urea was 151 mg. per 100 c.c. the protein excretion had risen to 1592 mg. per twelve hours, all the casts were of the renal failure type, there were 49,000,000 red blood cells, and the white blood and epithelial cells, previously within normal limits, increased to 1,750,000 per twelve hours. But he still was cheerful and carried on his work though now he was much distressed by sudden cramps in various muscle groups and was too weak to walk more than a short distance. In this manner he passed gradually into a state of lethargy and finally became comatose and died in October 1930.

The data are arranged in chronological order with short notations as to the clinical sequences in Table xxxv.

PATHOLOGICAL OBSERVATIONS

At autopsy a general arteriosclerosis involving the coronary, renal and cerebral arteries was found. In the right temporal lobe was a recent hemorrhage and in the region of the right caudate nucleus an area of softening. The heart was one and a half times its normal size. As terminal infections there were present a fibrous pericarditis and a bronchial pneumonia. The kidneys were reduced in size, measuring about 8 × 6 × 4 cm. Their capsules were adherent and stripped with difficulty, leaving a roughly granular reddish gray surface in which were several small cysts. On the cut surface the cortex appeared only 2 mm. in thickness and presented indistinct markings. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

A section of heart muscle showed a sclerosis of the arteries and small fibrous scars between the muscle fibers. Sections of arteries in various organs showed a marked thickening of their intima with degeneration.

KIDNEYS. *Glomeruli.* None of the glomeruli have retained their normal structure. Many, about one-quarter of the total number, are enlarged, their tufts are infiltrated with leucocytes, both mononuclear and polymorphonuclear, and the capillaries contain fibrin thrombi. In some of these Bowman's space is filled with a typical crescent while the capillary space in others is obliterated by fibrous adhesions. In still others there is a proliferation of connective tissue with obliteration of the tuft structures and some are completely transformed into masses of hyaline collagen. A few of the glomeruli show tufts which are more perfectly preserved but about these is a concentric periglomerular fibrosis.

Tubules. There is an extreme disarrangement of the tubules throughout the cortex. In large areas they are compressed and collapsed and lined with an atrophic epithelium. In many places they no longer exist as tubular structures but appear as clusters of distorted cells which are cross sections of solid cords. In other areas the tubules are dilated to several times their normal diameter and their lumens are filled with colloid material. Among such groups are well-developed cysts, the largest 2 mm. in diameter, which contained clear fluid and thus now appear empty. In all these dilated structures the epithelium is flattened to a low cuboidal lining which in many instances is almost endothelial in appearance. In scattered areas are other groups of tubules which have maintained their normal shape and arrangement. Of these many are increased in size and are lined with a thick hypertrophied epithelium. Many tubules of the various types that have been described show regressive changes of all sorts, such as cloudy swelling, fatty degeneration, and even necrosis with desquamation. In the lumen of the convoluted tubules and the broad ascending limbs of Henle's loop as well as in the collecting tubules are many hyaline, granular and epithelial casts. Other masses of detritus in the tubule lumen are calcified. In the ducts of Bellini are typical large renal failure casts.

Interstitial Tissue. Throughout the cortex there is an irregular patchy development of connective tissue. The entire architecture of the cortex is disarranged, areas of dense fibrosis and consequent tubular collapse and obliteration alternating with areas of lesser connective tissue development where the tubules and glomeruli retain to a more perfect degree their normal arrangement. This connective tissue is mostly fibrous, consisting of dense collagen, but throughout it are scattered areas of dense inflammatory round cell infiltration. In the medulla there is also a dense hyalinization of the interstitial tissue. There are also several areas of calcification and others of necrosis where the tissues have been infiltrated with gouty deposits. There is only a slight reaction in the tissues about these areas.

Blood Vessels. All of the arteries show a marked sclerosis. The large arcuate vessels show an extreme irregular fibrous thickening of their intima as do also the larger interlobular branches. Even the small vessels deep in the cortex are sclerosed

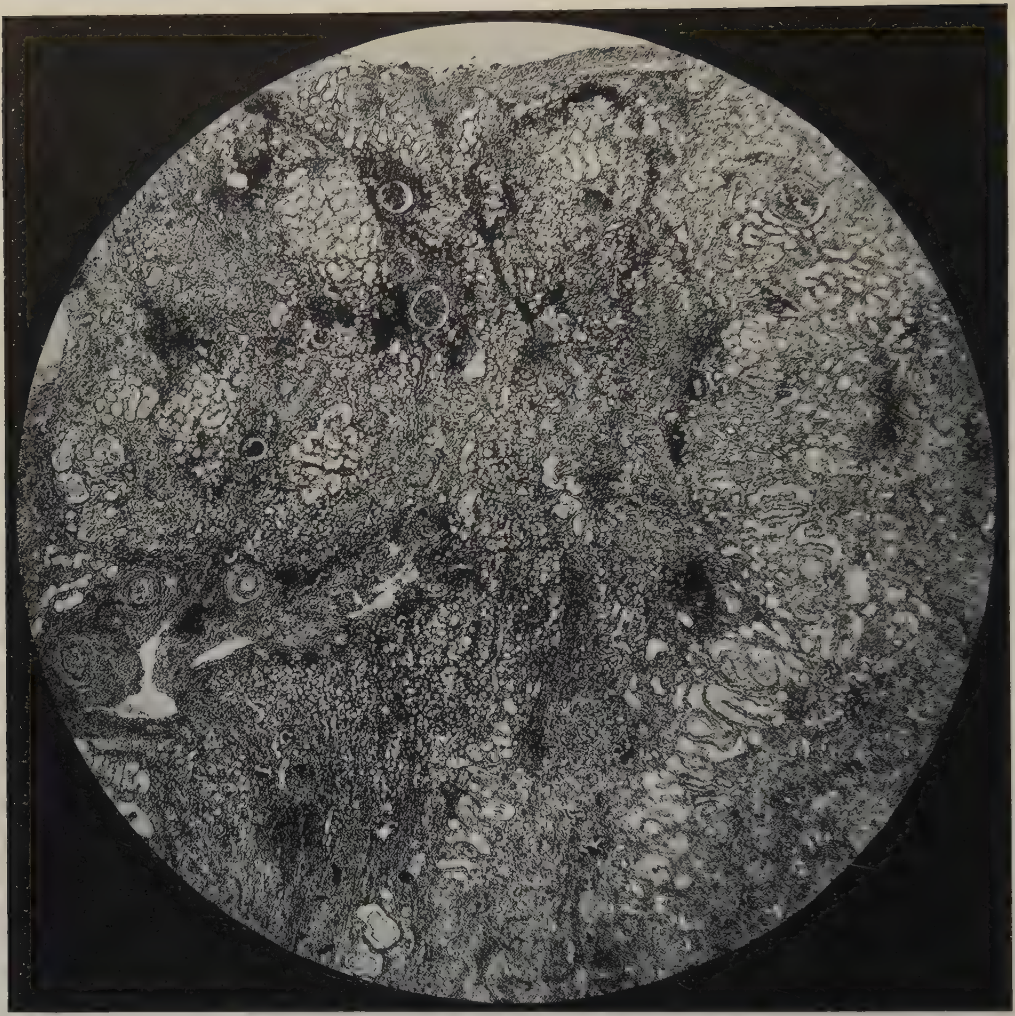

Plate XLVI a

The patchy disarrangement of the kidney architecture is seen with an occasional enlarged glomerulus remaining and alternating areas of tubular collapse and hypertrophy. The dark irregular spots in the interstitial tissue are areas of inflammatory leucocytic infiltration. The marked sclerosis of the arteries is well shown.

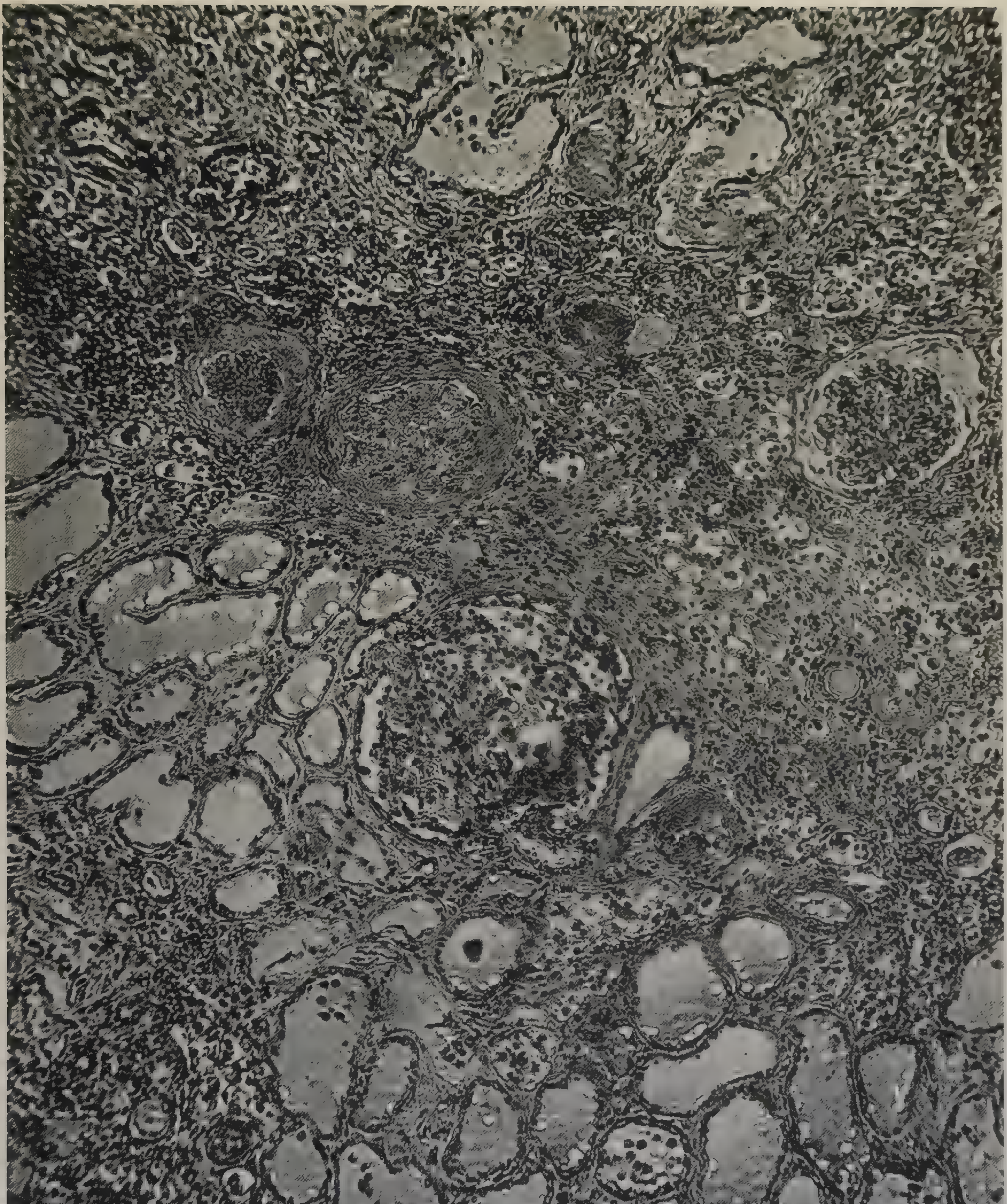

Plate XLVI b

Two glomeruli are seen, both showing active inflammatory lesions, the larger one, in the center of the figure, presenting a typical crescent. Below this tuft are seen the fibrous remains of two other glomeruli. The distortion of the tubules is very evident as well as the leucocytic infiltration of the interstitial tissue.

down to and including the afferent arterioles of the glomeruli. Many of these small cortical branches are practically occluded by the extreme hyaline thickening of their walls.

SUMMARY

The kidneys show a marked involvement of the glomeruli by inflammatory lesions which vary in nature from early to late stages of the processes. The tubules present marked degeneration and atrophic changes which, combined with the patchy inflammatory involvement of the interstitial tissue, has produced a marked alteration of the kidney architecture. There is also an extreme sclerosis of the arteries and arterioles. Renal failure casts are present. Associated with these renal lesions was a severe general arteriosclerosis and gouty deposits.

Degenerative Bright's Disease

THE CRYPTIC FORM

CASE XLVII

George D. Aged thirty-three.

Clinical Diagnosis. Degenerative Bright's disease, cryptic form.

Duration. Six months. Observed two days before death.

Etiology. Unknown.

Course. On September 1, 1922 edema appeared during a period of severe physical work with insufficient food. The edema persisted during the next four months in spite of rest and successive low calorie and high protein diets. During December 1922 and January and February 1923 he was in a hospital where it was observed that the urine was deeply colored, highly albuminous and that it contained a large number of casts with few or no red blood cells. There was no evidence of arterial disease. Under vigorous treatment the edema diminished but he became progressively weaker and more emaciated and died on February 28, 1923 with evidences of a terminal infection.

RELEVANT CLINICAL DETAILS

This patient was seen only once, two days before he died. We are indebted to Dr. LeRoy H. Briggs for the history and for the observations he made.

During childhood there had been no infections other than the milder exanthemata. There was no history of scarlet fever or of tonsillitis. At the university he had been considered unusually perfect from a physical point of view. He rowed for the university and a transient albuminuria had been found after races but at no other time.

He remained in excellent health until he was thirty-three years old. He happened then to be working at a mine where a fire had trapped a large number of men and for several days he worked practically continuously under great extremes of temperature and with little food but whiskey and coffee. Immediately after this occurrence on September 1, 1922 he first noticed that his feet and ankles were slightly swollen. He is quite certain that there were no other symptoms apart from the exhaustion natural after his exertions. The edema gradually increased until his thighs became swollen. He then consulted a doctor at the mine who told him he had nephritis and put him on a "low diet." The edema however increased rather than diminished. He then went on a long fishing trip in the Sierras and during this period lived mainly on meat and fish. The swelling decreased but his legs, hands and genitals remained always quite definitely swollen. After a subsequent period of fruitless treatment in the country he came to San Francisco to be under the care of Dr. LeRoy H. Briggs.

On December 9, 1922, Dr. Briggs found that the urine was deeply colored but not smoky. The sediment contained a large number of casts. He was edematous from the waist down and there was fluid in both pleural cavities and a moderate ascites. The heart seemed to be enlarged to the left, the blood pressure was 140

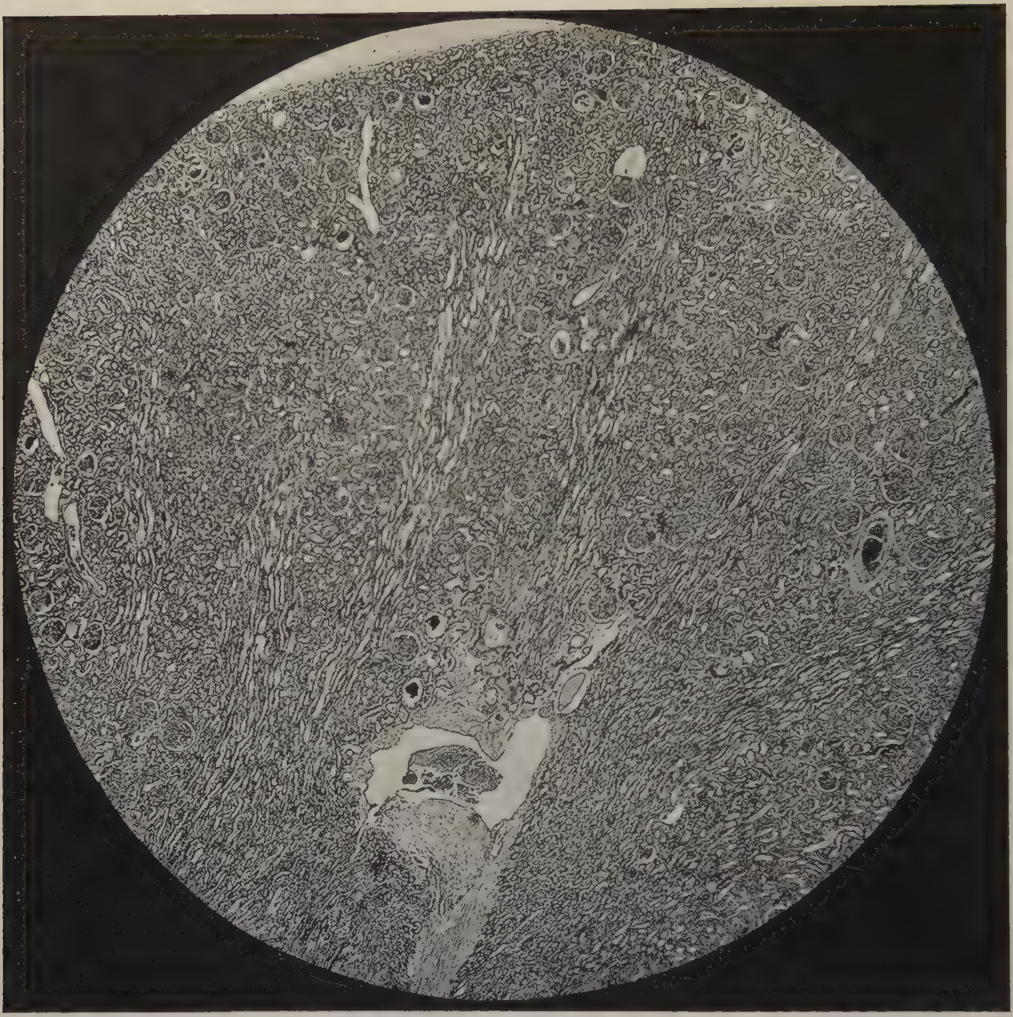

Plate XLVII a

The section appears much like a normal kidney at this magnification since the only significant lesions are degenerative ones in the tubular epithelium. The glomeruli, interstitial tissue and arteries are essentially normal.

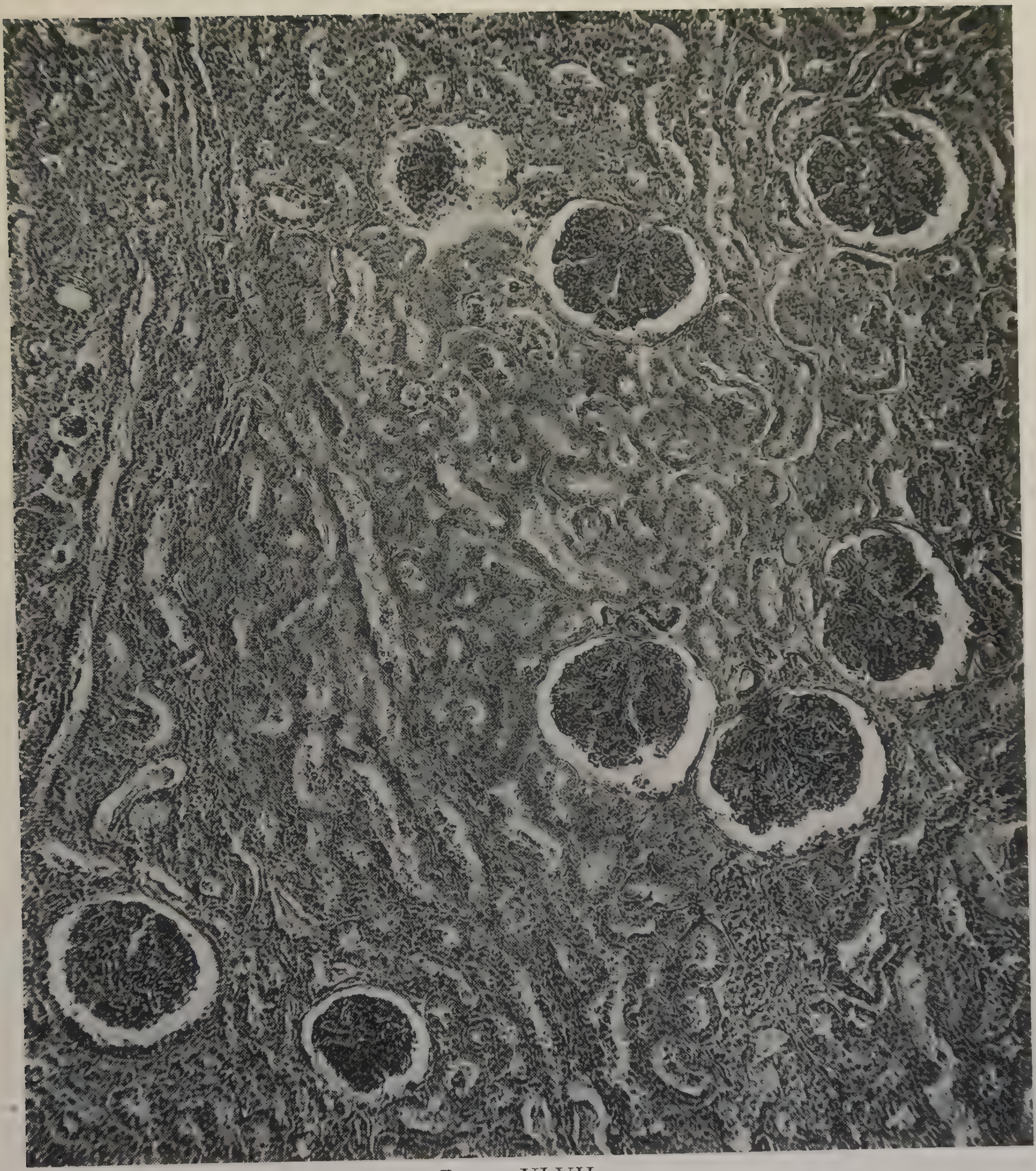

Plate XLVII b

The glomeruli show no significant lesions nor are there definite inflammatory changes in the interstitial tissue. There is a marked cloudy swelling of the epithelium of the convoluted tubules.

systolic and 80 diastolic. There was no thickening of the peripheral arteries and the retinal arteries were normal. There was no anemia. A blood count gave 5,120,000 red blood cells per cubic millimeter.

He was put on a Karell diet, daily sweat baths and 30 gm. of magnesium sulphate in saturated solution. By December 18 there was a marked decrease in the subcutaneous edema and much less fluid in the pleural cavities. The urine was still deeply pigmented and contained albumin in large amount with tremendous numbers of casts but no red blood cells. There was a slight elevation of temperature. A piece of buttered toast was given daily in addition to the milk. On December 21 his febrile attack had subsided, and there was only a trace of edema over the sacrum and around the ankles. Some potatoes, custard, and cereal were added to the diet. But on December 26 there was an increase in the fluid in the chest and abdomen and the number of casts and the amount of albumin seemed to have increased. By January 3, 1923 the edema had greatly augmented and he was put back on a strict Karell diet, and by January 16 there was much less edema. He was then put on unlimited carbohydrates but the ascites and edema of the legs increased. On a general unrestricted diet there was a further increase in edema and after three days he was put back on the Karell diet. The non-protein nitrogen concentration at this time (January 16, 1923) was 82 mg. and the blood urea concentration 46 mg. per 100 c.c. Digitalis and calcium chloride were given without effect. On January 25 the urine had a specific gravity of 1.030 and the sediment contained many casts sprinkled over with fat droplets. By February 8 the abdomen had become densely swollen and 3½ gallons of fluid were removed. A pressure sore had developed on the right hip. He was extremely emaciated.

He was seen for the first and only time on February 28, forty-eight hours before his death. He was then in a moribund condition, extremely cachectic and with numerous skin pustules and hemorrhages. It was not possible to obtain a timed urine collection, but a specimen which was saved was found to contain a large number of narrow hyaline casts sprinkled with fat droplets, many of which were doubly refractile. In some ascitic fluid obtained just before death the concentration of urea was 643 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained after death. They were of normal size measuring 12 × 6 × 4 cm. Their capsules stripped easily leaving a smooth greyish pink surface. Except for some cloudiness of the cortex the cut surface appeared normal. The arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. None of the glomeruli show any significant lesions. There is no increase in the number of nuclei in the tuft nor any proliferative changes. The capsular space is free of fibrinous exudate, though in the most cases there is a small amount of granular material in it.

Tubules. There is a very marked cloudy swelling of the epithelium of the convoluted tubules and of the broad ascending limbs of Henle's loop. The degeneration is of the mild type, that is, the protoplasm of the cells is increased in bulk and has a ground glass appearance without any very definite accumulation of granules. The nuclei are well preserved, though occasionally necrosis and desquamation have occurred. Practically every convoluted tubule in the cortex is filled with granular or semihyaline coagulated material. In the straight tubules definite hyaline casts are present, almost every tubule section containing such a plug. No renal failure casts or blood casts are present.

Interstitial Tissue. The interstitial tissue is normal except for occasional small fibrous scars in which are a few round cells. In the medulla there are small patches of edema in the intertubular connective tissue.

Arteries. The arteries are entirely normal.

SUMMARY

The kidney is normal except for the active degenerative process in its epithelium and for the casts which fill its tubules. There is also evidence of glomerular leakage of protein in the coagulated material found in Bowman's space.

CASE XLVIII

Otis E. Aged fifty.

Clinical Diagnosis. Degenerative Bright's disease, cryptic form.

Duration. Ten months. Observed during the last four and a half months.

Etiology. Unknown.

Course. Edema unaccompanied by other symptoms and not preceded by any illness appeared in April 1924 in a degree which was soon sufficient to disable him mechanically. During May, June and July the urine is known to have contained much albumin but at no time was more than an occasional red blood cell seen in the urinary sediment. When seen for the first time in September the sediment was free from red blood cells and blood casts but contained a large number of hyaline casts sprinkled with fat droplets and many epithelial cells. He died in an extremely asthenic state four and a half months later.

RELEVANT CLINICAL DETAILS

Edema was the outstanding symptom in this case. It was noted first on April 30, 1924 when he found to his surprise that his feet and ankles were swollen. Since there were no other symptoms he continued his work as a pharmacist, but within ten days he was obliged to stay in bed, not because he felt ill but simply because the edema increased so rapidly that he found it more and more difficult to walk.

The history of his previous illnesses was somewhat involved but it was not possible to obtain any plausible explanation for the sudden onset of an extreme anasarca. In August 1923, nine months before the edema was first seen, thirst, polyuria and increased appetite had developed. These symptoms were followed by loss of weight and general weakness, but as his weight decreased the other symptoms disappeared so that for a period of six months or so before the edema was noted he was not conscious of more than a slight asthenia and was sure that he had suffered from no acute illness or infection. The only noteworthy incident during that time was the extraction of all his remaining teeth on account of a long-standing pyorrhea, an operation which he quite successfully withstood in spite of his rather weakened condition. Still further back in his history a long series of throat infections is recorded which ended with a tonsillectomy in 1918. In 1908, when he was thirty-five years old, the typical syndrome of Graves' disease developed and continued in varying degree until 1914 when the greater part of his thyroid gland was excised. It was during this period that a persistent but obscure skin lesion appeared which continued to trouble him at intervals even after the symptoms of Graves' disease had disappeared. In addition to all these afflictions he had been for many years an almost constant sufferer from various dyspeptic symptoms and as a consequence he had fallen into the habit of avoiding a large variety of foods which he believed he could not digest.

It is fortunate that at the very beginning of his terminal illness, ten days after the onset of the edema, he was admitted to the Woodland Clinic where observations of his condition at that time and on two other occasions during the next three and a half months were carefully noted. There was then a pronounced edema of the legs and genitalia and considerable collections of fluid in the abdominal cavity and in both pleural cavities, especially on the left side. The heart was somewhat enlarged to the left, the arteries were regarded as thickened, the blood pressure was 154 systolic and 92 diastolic. The urine contained 1.4 per cent of sugar but next morning the blood sugar was only 145 mg. per 100 c.c. On a diet containing 45 gm. of carbohydrate and 60 gm. of protein the subsequent twenty-four hour urine collections were found free from sugar.

There are reports of urine examinations on six of the seven days he spent at the Woodland Clinic between May 9 and 16, 1924. In each instance large amounts of albumin were found and in the sediment hyaline and granular casts. In three instances there was no mention of blood and in the other three specimens the presence of an "occasional red blood cell" was noted. The blood urea concentration was 22 mg. per 100 c.c.

The pleural cavities were drained. The fluid (750 c.c. from the left side and 100 c.c. from the right) was clear and "almost water-white in color." An unknown quantity of fluid was removed from the abdominal cavity. A quantitative diet low in carbohydrate and in salt was given.

On June 3 the patient reentered the Woodland Clinic in a still weaker condition. The edema was as pronounced as before. From the left chest 1200 c.c. of the same kind of fluid were obtained, 1250 c.c. from the right side, and 4100 c.c. from the abdomen. The urine was unchanged, only some specimens containing a few red blood cells. The blood urea concentration was 40 mg. per 100 c.c.

The patient's diet was increased and he was given insulin. He left the Woodland Clinic considerably improved on June 22, though there was still a pronounced edema of the legs.

During July he reported by letter that the improvement in his condition was continuing and his strength increasing. He estimated that he lost about 5 gallons of fluid from puncture wounds made in his legs and groins, but on July 31 he returned to have fluid removed from both pleural cavities and from his abdomen.

He came to San Francisco on August 30, 1924, four months after he first saw the beginning of the swelling of his legs. At that time he was still in much the same state as when he entered the Woodland Clinic. There was general anasarca with an almost maximal edema of the lower extremities, a small amount of fluid in both pleural cavities and a considerable collection in the abdomen. Although he had a somewhat anemic appearance his red blood cells numbered 4,680,000 per cubic millimeter. There were 13,000 white blood cells but only 61 per cent of polymorphonuclear cells. The basal metabolism was -16 per cent on his actual weight but -2 per cent when calculated for what was estimated as his weight without edema. There was no evidence of cardiac enlargement. The pulse was rapid (96–110) but regular. The systolic blood pressure was 130, the diastolic 90. The peripheral ar-

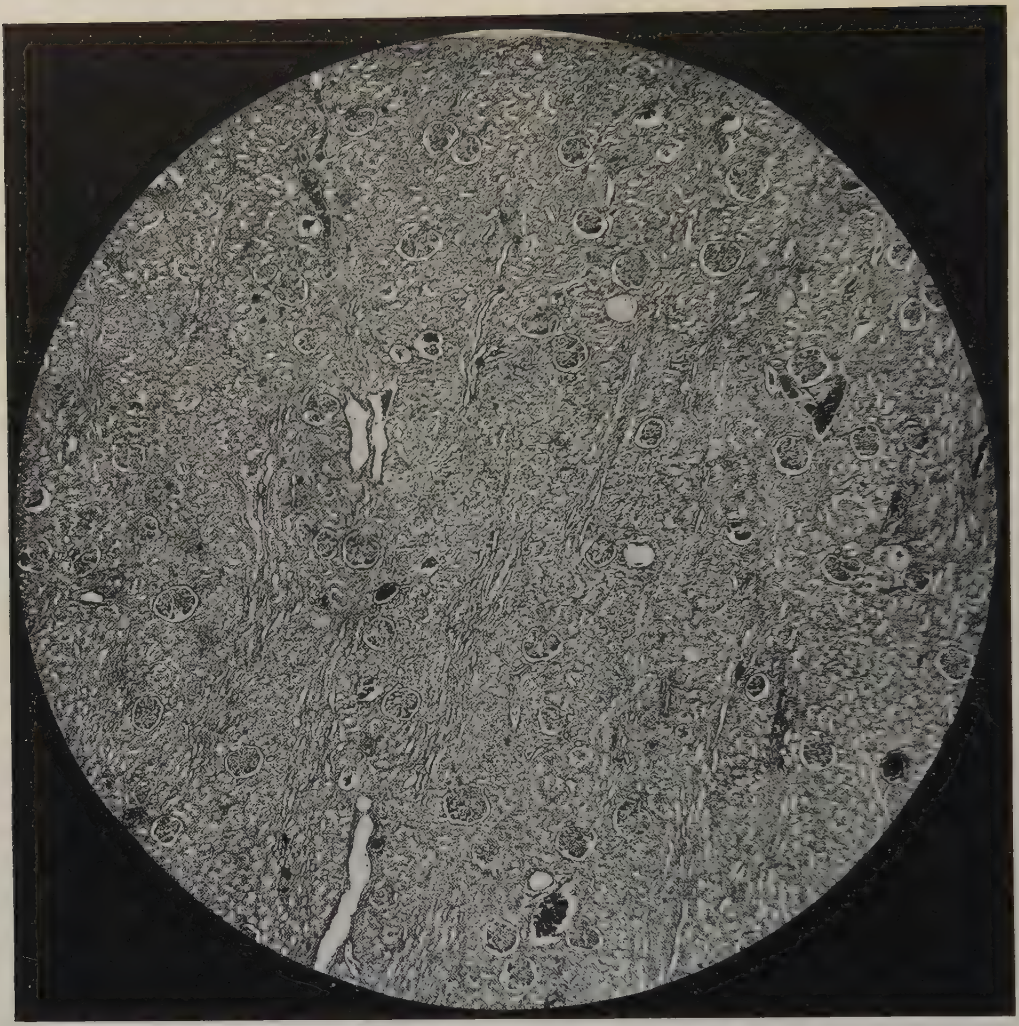

Plate XLVIII a

The lack of pathological changes in the glomeruli, interstitial tissue and arteries produces an appearance at this magnification which differs little from normal.

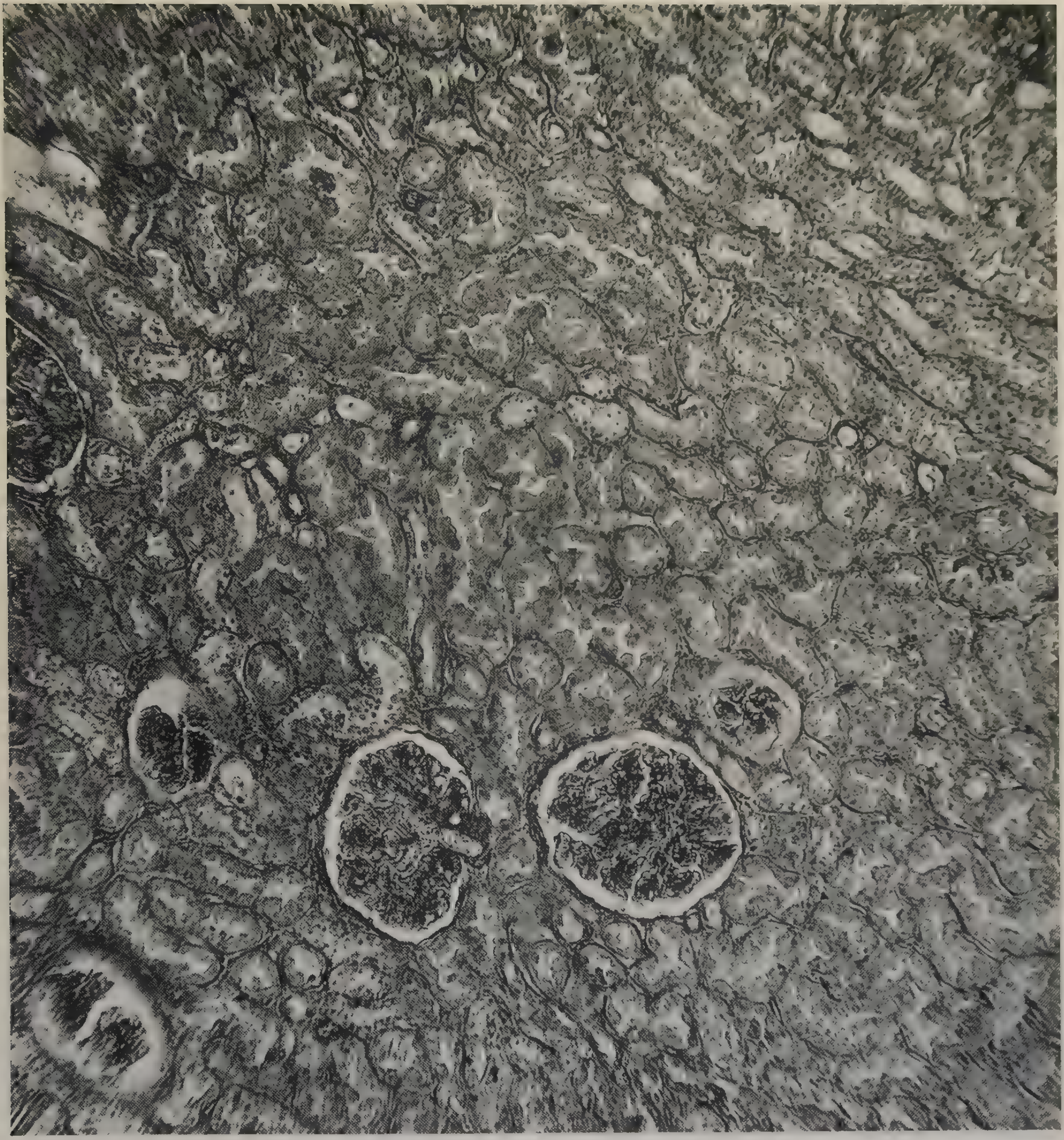

Plate XLVIII b

There is a marked cloudy swelling of the epithelial cells of the convoluted tubules. Otherwise no significant lesions are seen. (Cf. Plate lxxv.)

teries were not regarded as thickened and an oculist reported that he considered that the retinal arteries were normal. The Wassermann reaction was negative.

A concentration test had a volume of 260 c.c. of clear amber-colored urine. The specific gravity was 1.024. The rate of protein excretion was 3070 mg. per twelve hours. The sediment contained an unusually large number of cells, almost all of which seemed to be epithelial cells. The number estimated was 27,200,000 per twelve hour period. Many of them contained fat droplets or large granules. In spite of a careful search no red blood cells could be found. The number of casts was 807,000 and of these 5 per cent were fatty and the remainder were hyaline casts studded with many shining fat droplets. The picture then was one which suggested a renal degeneration which was in part at least a fatty degeneration. It was well that these fact were ascertained because in the course of a catheter collection of urine for bacteriological purposes an infection was set up which prevented any accurate counts thereafter.

Several attempts were made to measure the amount of secreting renal tissue, but urea and large amounts of water completely failed to produce any appreciable increase in urine volume and the results were therefore unreliable. But the following series of blood urea concentrations suggest that there was an extensive though not a progressively advancing disablement of the secreting tissue of the kidney:

TABLE XXXVI

	Date	*Blood Urea Mg. per 100 C.c.*
1924	Sept. 1	71
	Sept. 17	76
	Nov. 6	51
	Dec. 3	44
	Dec. 13	57
1925	Jan. 28	54
	Jan. 31	60

The blood plasma was milky and throughout the entire course of observation the ascitic and pleural fluids maintained their watered milk appearance.

There was a rapid decrease but never a complete disappearance of subcutaneous edema. In two months his weight fell from 152 to 104 lbs. with one tapping of the peritoneal cavity at which 3750 c.c. of fluid were removed. The extreme emaciation was then apparent. Yet it was very difficult to get him to eat, even though considerable doses of insulin were given.

In spite of the decrease in subcutaneous edema, fluid continued to collect in the peritoneal and pleural cavities. Between September 10, 1924 and February 11, 1925, 59,300 c.c. of fluid were withdrawn, an amount whose weight exceeded the patient's body weight. During twenty-three days of January 1925, 28,900 c.c. of ascetic fluid were removed which indicates that the transudate formed at the rate of about 1300 c.c. a day. The absolute amount of protein lost in this way was not large for the protein concentration of the fluid was low, about 150 mg. per 100 c.c. Nor was the daily loss of protein in the urine great as compared with many other cases. The average loss for twenty-four hours was only 4.5 gm.

The patient's condition remained essentially the same until the end except for a growing disinclination for food and an advancing asthenia. The blood pressure tended to fall, the extremities became blue and cold. He was very apathetic but quite rational. During the last few days his temperature became subnormal and he seemed to die of starvation.

PATHOLOGICAL OBSERVATIONS

Only the kidneys and a piece of liver and spleen were obtained at autopsy.

The kidneys were normal in size, measuring about 12 × 6 × 4 cm. Their capsules stripped easily, leaving a smooth light grey surface in which were some remnants of the fetal lobulations. The cut surface showed a definite widening of the cortex. The medulla and pelvis and renal arteries appeared normal.

The pieces of spleen and liver showed no gross lesions.

MICROSCOPICAL EXAMINATION

Sections of spleen showed a moderate hyaline degeneration of the arteries. The sections of the liver were normal.

KIDNEYS: *Glomeruli.* Practically all the glomeruli in all the sections are normal. The capillaries are filled with blood, the tufts are not fibrous and Bowman's space is empty. Occasionally a hyaline glomerulus is seen lying in one of the few small scars that are scattered throughout the cortex.

Tubules. The shape and course of the convoluted tubules in the cortex is normal, but their diameter is increased. This is due to a marked increase in the size of their epithelium. The cells are swollen and their protoplasm filled with fine granules. The nuclei appear normal, though in some places there is a slight desquamation of the cells. Irregularly scattered through the cortex are groups of tubules where cells are filled with fine fat droplets. The lumens of the tubules are more or less decreased by the swelling of the epithelium and contain granular debris and occasionally a hyaline cast, but no red blood cells are seen.

The broad ascending limbs of Henle's loop show the same changes, while the collecting tubules, except for an occasional cast, are normal.

Interstitial Tissue. The interstitial tissue throughout the cortex is entirely normal except in a few isolated spots where there is a small fibrous scar. These are insignificant in number, however, as compared to the amount of normal tissue.

Arteries. There is a moderate fibrous thickening of the intima of the arteries.

SUMMARY

The only lesions of any significance in the kidneys are degenerative. These consist of a severe widespread cloudy swelling and a scattered fatty degeneration of the epithelium of the convoluted tubules. There is no evidence of any significant inflammatory process in any element of the kidney.

CASE XLIX

Mildred F. Aged twenty-one.

Clinical Diagnosis. Degenerative Bright's disease, cryptic form.

Duration. Fifteen months. Observed for six months.

Etiology. Unknown.

Course. An unexplained edema and albuminuria came and went during November 1919. In January 1920 both of these symptoms recurred and by March there was massive anasarca and the rate of protein excretion reached unusually high levels. The urinary sediment gave evidence only of tubule degeneration and desquamation. The albuminuria gradually decreased, the edema was absorbed, and by September 1920 there was only occasionally a slight swelling of the ankles. Thereafter she was free from edema up to the time of her death in February 1921 from carbon monoxide poisoning.

RELEVANT CLINICAL DETAILS

During the first week of November 1919 an edema which was first noted in the ankles rapidly increased and extended over the entire body. Albuminuria was the only other symptom. Although she had not felt quite well since a mild attack of influenza eleven months before, there had been no aggravation of the headaches, dizziness and palpitations from which she at times suffered. She spoke indeed of "chills and fever" experienced one day about a week before the edema appeared, but as her temperature had not been measured, and the sensation was only transient, it seems likely that this description referred only to a manifestation of her vasomotor instability. Within a month the edema had gone and her doctor told her that the albuminuria also had disappeared.

In January 1920 at a time when she was feeling stronger than usual she again noticed swelling around her ankles. She immediately stopped work and stayed in bed. Two days later she had for a day a fever which rose as high as 100°F. and she suffered from nausea and severe headache. Thereafter the temperature remained normal but the edema continued slowly to increase and to extend from her legs over her body in spite of rest in bed and salt low food. The doctor told her that the urine contained large amounts of albumin. There were no other symptoms.

She was first seen in March 1920. By that time her legs were enormously swollen and a deeply pitting edema extended as far as the thorax, but was only present in slight degree in the arms and face. The abdominal cavity contained a large amount of free fluid and there were evidences of the presence of fluid in both pleural cavities. No abnormality was detected in the heart or vessels. The systolic pressure was 100 and the diastolic 80, and throughout the whole period of observation the pressure readings remained below the normal average. The blood urea concentration was 15 mg. per 100 c.c. The urine contained a large amount of albumin. In one twelve hour period 12.6 gm. of protein were excreted. No counts were made but it did not appear that red blood cells were present in appreciably greater numbers than may be found in normal urine. There was however a marked increase in epithelial cells and epithelial, granular and fatty casts were seen. In none of the many specimens examined were any blood casts found. Embedded in the hyaline and fatty casts and lying free in the sediment were many doubly refractile fat droplets.

A few days later there was fever for three days. On one day the temperature rose to 104°F. She complained of pain in the right thigh and on examination some redness of the skin was noted on the inner aspect of the thigh. There was acute tenderness and an augmentation of the edema. The white blood cells rose to 26,000 per cubic millimeter with 82 per cent of polymorphonuclear leucocytes, but no organisms were grown from urine and blood taken at the height of the fever. A thrombosis in the internal saphenous vein was regarded as the most probable cause. Within four days all signs of disturbance had disappeared.

During March and April the edema rapidly decreased and the albuminuria diminished but did not entirely disappear. Towards the end of April the amount of functioning renal tissue was 93 per cent of the normal as estimated from the results of the urea ratio test.

In May the patient left San Francisco, still with a slight edema and albuminuria. She subsequently became entirely free from edema but up to September she reported occasional slight recurrences. From that time she no longer answered letters and was not heard of again until February 1921 when her death from carbon monoxide poisoning was reported. Her father stated that for six months edema had not been seen. Unfortunately no urine was found in the bladder at the postmortem examination, so it is not known whether the albuminuria had also disappeared.

PATHOLOGICAL OBSERVATIONS

At autopsy the typical cherry red discoloration of carbon monoxide poisoning was found. There was no edema. The internal organs were entirely normal, the heart being of normal size. Both kidneys were identical in appearance. They were of normal size, measuring 12.5 × 6 × 4 cm. Their capsules stripped easily, leaving a smooth surface of normal appearance except for some pinkish discoloration. The cut surfaces of both kidneys also showed no gross lesions and the renal arteries as well as the general arterial system was entirely normal.

MICROSCOPICAL EXAMINATION

Glomeruli. The glomeruli throughout the sections are essentially normal. Rarely a small amount of granular material is seen in Bowman's space, but the capillaries of the tufts are not involved.

Tubules. The convoluted tubules in the cortex are enlarged. This is due to a moderate but definite swelling of the epithelial cells, the protoplasm is finely granular but the nuclei are well preserved and there is no evidence of necrosis. In the broad ascending limbs of Henle's loops the degenerative processes are more

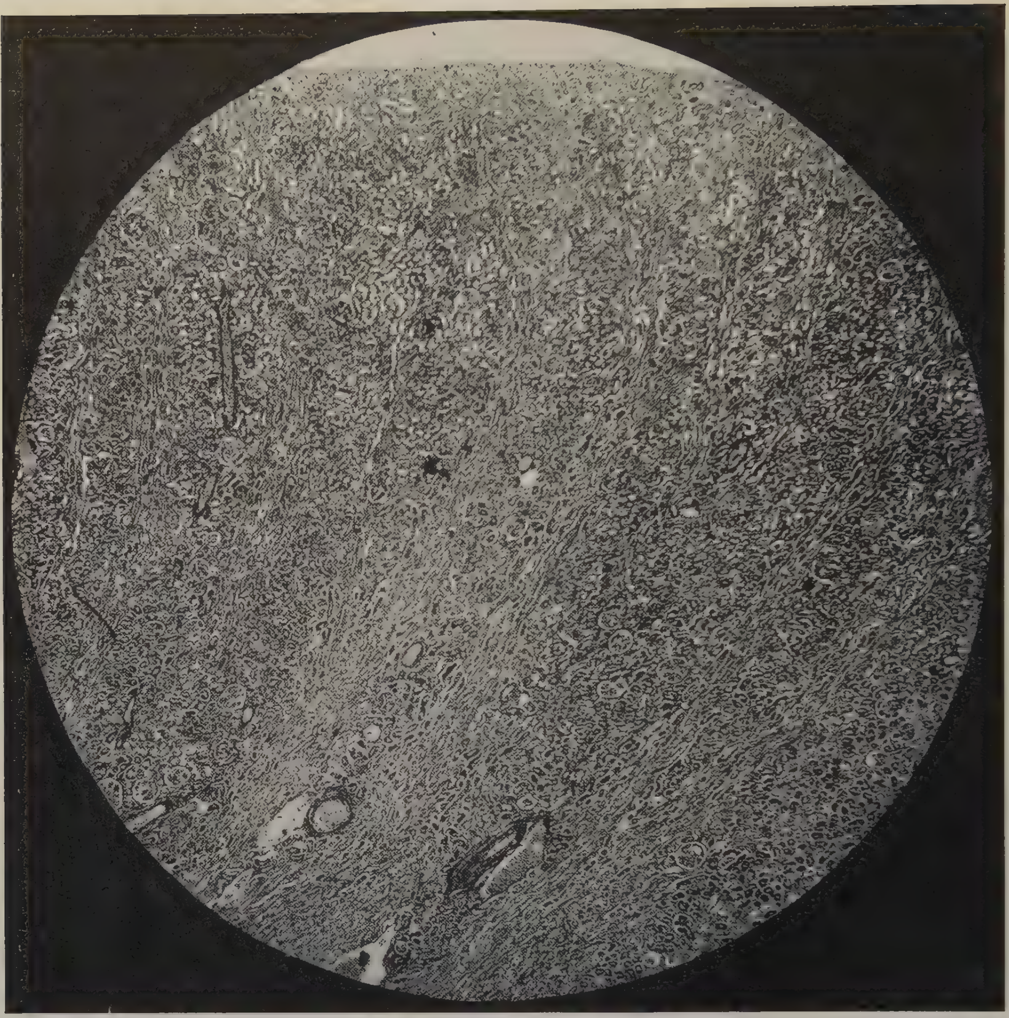

Plate XLIX a

The marked regressive changes of degeneration and necrosis in the tubular epithelium produce an irregular blotchiness in the section. Otherwise since the glomeruli, arteries and interstitial tissue show no lesions, the general appearance of the section is normal.

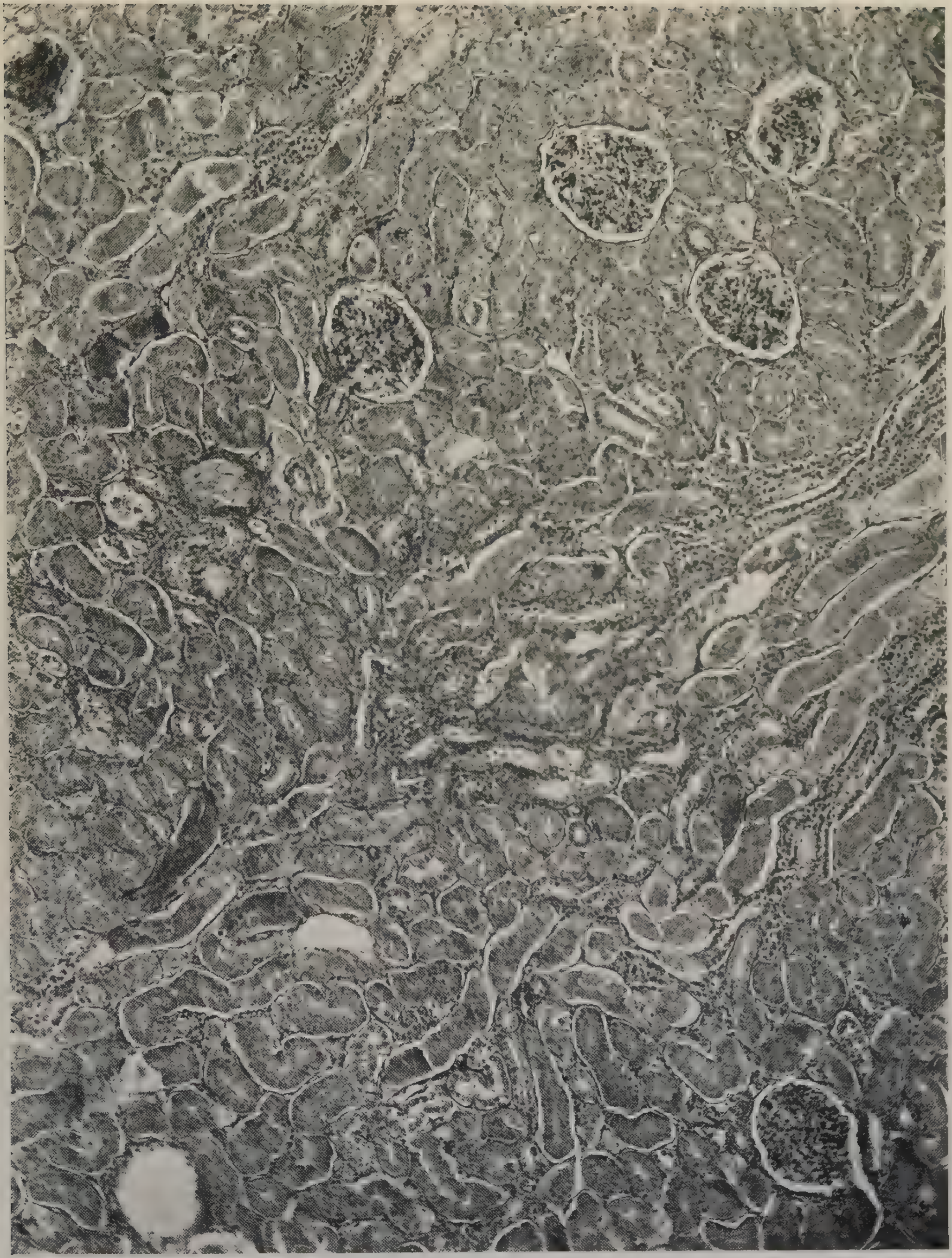

Plate XLIX b

The glomeruli are normal. The tubular epithelium shows degenerative processes varying from marked cloudy swelling to a definite necrosis. A group of necrotic loops of Henle may be seen in the right center portion of the figure. The interstitial tissue is normal. (Cf. Plate lxxvi.)

pronounced. All show a cloudy swelling, while in many there is frank necrosis with disappearance of the nuclei and desquamation of the cells. In others of these ascending limbs there is evidence of repair, since the tubules are filled almost completely with new-formed small dark regenerated epithelium.* The collecting tubules are normal. An occasional hyaline cast may be found in their lumens.

Interstitial Tissue. The interstitial tissue is entirely normal. There is no proliferation of its connective tissue nor round cell infiltration.

Arteries. The arteries are normal.

SUMMARY

The kidneys show only slight abnormalities, and these consist of epithelial degeneration of the convoluted tubules and necrosis of the ascending limbs of Henle's loop. There is an accompanying regeneration in the later regions but no inflammatory lesions are present in any of the renal elements.

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* It is obvious that the repair of the necrosis in the ascending limbs of Henle's loop proves that the destructive lesions antedated the terminal carbon monoxide poisoning.

CASE L

David R. Aged sixty.

Clinical Diagnosis. (1) Degenerative Bright's disease, cryptic form. (2) Renal arteriosclerosis.

Duration. Five months. Observed during the last four months.

Etiology. Unknown.

Course. The patient came to the clinic on account of a generalized edema which had appeared without obvious cause and within three weeks had become so pronounced that he could walk only with difficulty. The blood pressure was 165 systolic and 80 diastolic. The blood urea concentration was 63 mg. per 100 c.c. The urine, which some months before had been free from albumin, now contained as much as 16,000 mg. of protein in a twelve hour collection, and very large numbers of casts including epithelial, granular, and waxy casts. There were no blood casts and few red blood cells. This condition remained essentially unaltered until his death from cardiac failure five months after the onset of the edema.

RELEVANT CLINICAL DETAILS

The patient was a laborer, sixty years of age, who had been strong and well until 1917 when he visited the out-patient department because of tinnitus. The Wassermann reaction was positive but he did not come back until January 1920 when a course of antiluetic treatment was commenced. On January 19, 1920, and on February 2, 1920, no albumin was found in the urine. From January 1920 to April 20, 1920 fourteen doses of arsphenamine and seven intramuscular injections of gray oil were given. He complained of palpitation after the first injection of neoarsphenamine and a cardiac arhythmia was noted, but thereafter he had no complaints. He was not seen again until shortly after the commencement of his final illness five months later.

On October 9, 1920, he was brought to the hospital with an extreme edema of the lower extremities, slight edema of the subcutaneous tissues of the upper part of the body and a considerable collection of fluid in the abdominal cavity. He stated that three weeks previously he had noticed that his ankles were swollen. Within a week the swelling had extended to his waist line. Since he felt perfectly well he continued his work in the fields and only stopped when the weight of the swelling made it more and more difficult for him to move. For a few days there was some frequency of urination and on this account he looked at the urine but was unable to see anything unusual in its appearance.

The physical examination on entrance to the hospital showed no noteworthy abnormalities except for the edema, and an elongation of the aorta revealed by the *x*-rays. The systolic pressure was 165, the diastolic 80. The pulse was slow and regular.

Many cast counts were made on hourly specimens of urine. The number found was always large, the maximum reaching a total of 6,000,000 calculated for a

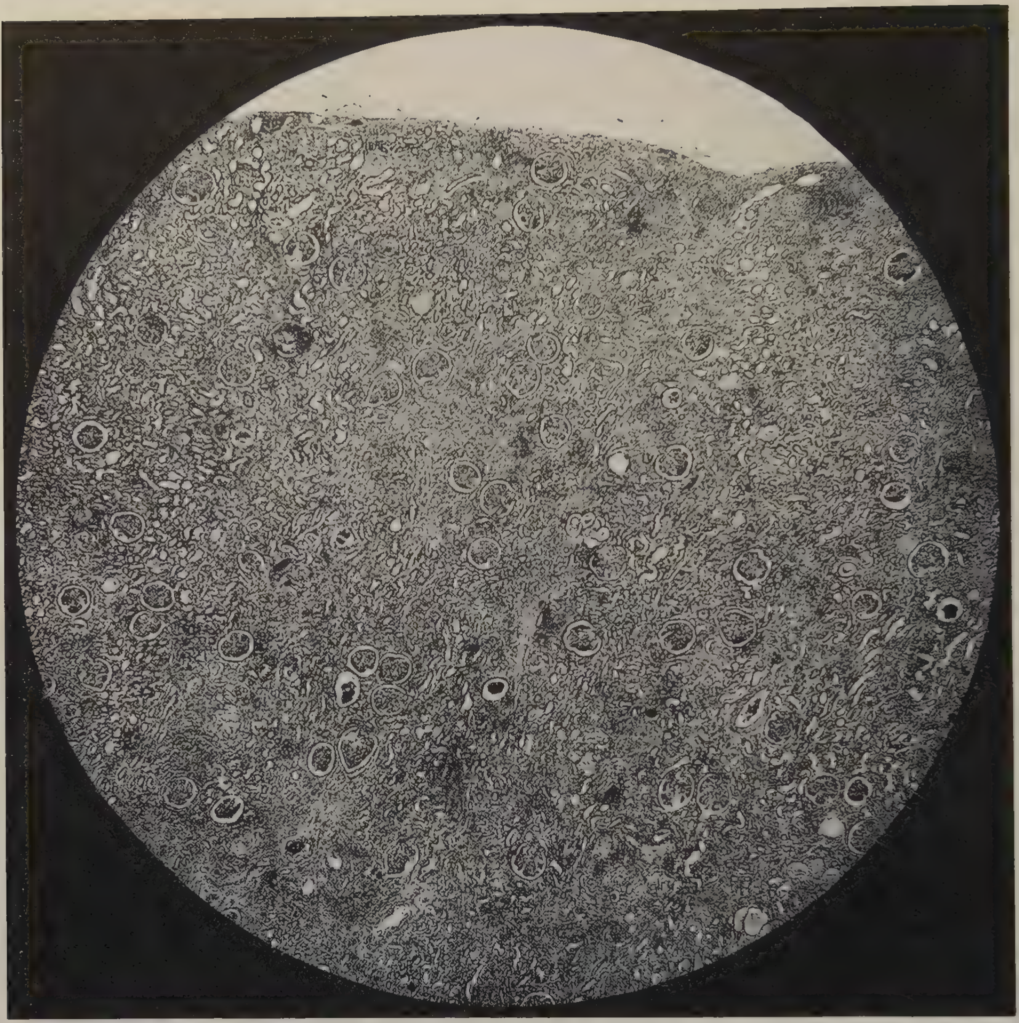

Plate L a

The glomeruli are well preserved. There is, however, a definite diffuse proliferation of the connective tissue throughout the cortex with scattered dark areas of round cell infiltration. Beside the degenerative changes in the tubular epithelium, which do not show at this magnification, there is a very definite distortion and atrophy of the tubules.

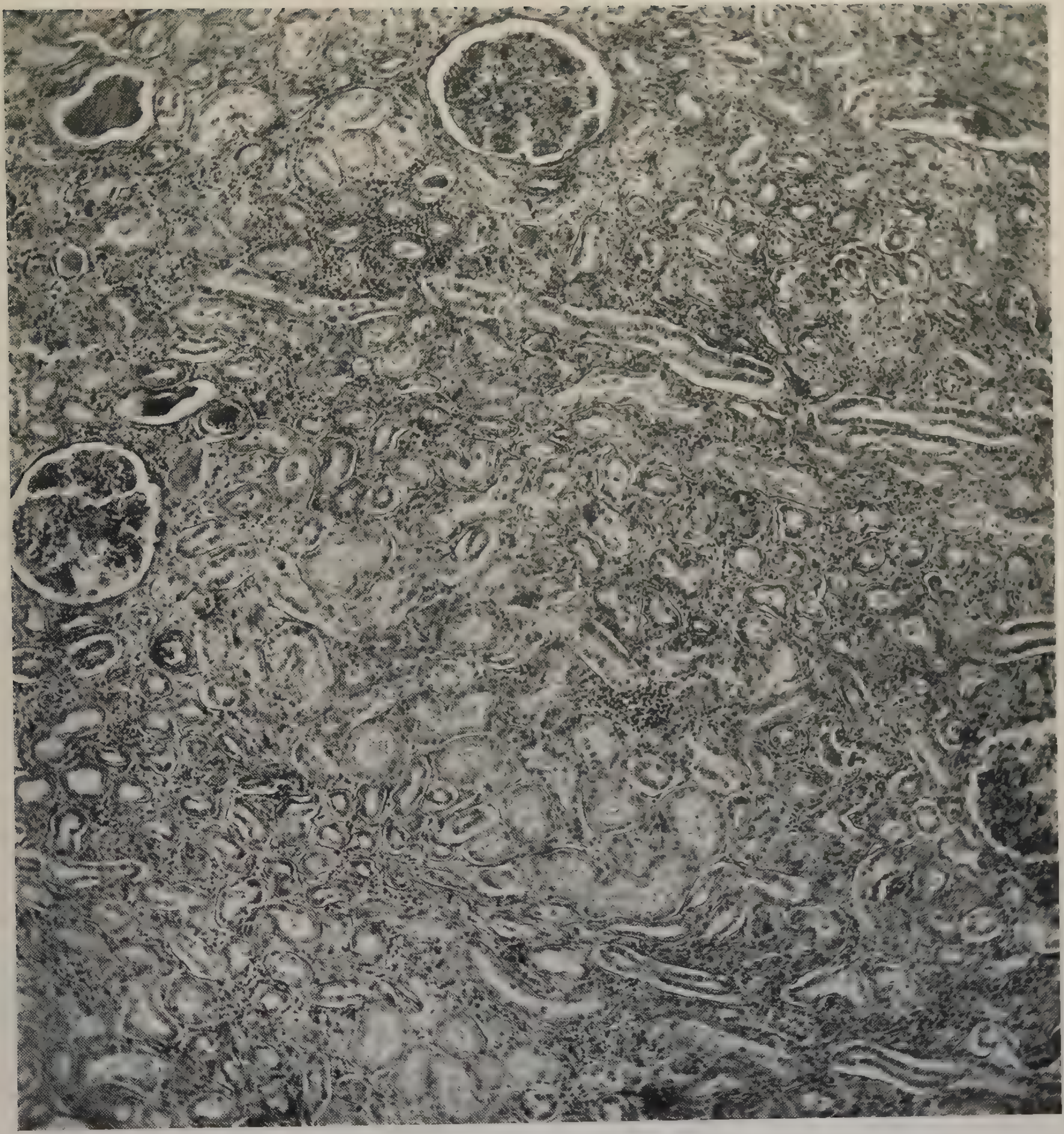

PLATE L B

There are no very definite inflammatory changes in the glomeruli. Throughout the interstitial tissue is a diffuse round cell infiltration and some proliferative change. The tubular epithelium shows all forms of degeneration and even necrosis. Many tubules are lined with new formed atypical regenerative cells. (Cf. Plate LXXVII.)

twelve hour period. No blood casts were seen among the many thousands of casts which were counted. Differential cast counts showed that as a rule from 80 to 95 per cent of the casts were hyaline and that many of them contained fat droplets, some of which were doubly refractile. After the administration of 5 gm. of cholesterol by mouth the number of refractile fat droplets was greatly increased. The remaining casts were epithelial, granular, waxy and fatty. Although no counts were made it was noted that the number of epithelial cells was greatly increased, and that few red blood cells were to be found. The rate of protein excretion during October, as determined from short time urine collections, averaged 18,320 mg. per twelve hours with a range of variation from 6120 mg. to 38,800 mg.

The amount of functioning renal tissue could not be determined with any accuracy because it was found to be impossible to induce diuresis by urea and water. But since the blood urea concentration was found to be 63 mg. per 100 c.c. it is probable that more than half of the renal tissue was not functioning.

These findings seemed to indicate that the kidneys were the seat of a very active degeneration. It seemed likely also from the patient's age and history, and from the presence of a moderate degree of hypertension, that this degenerative process had involved kidneys which had already been partially atrophied by renal arteriosclerosis. But the etiology of the degenerative process remained entirely obscure. It did not seem reasonable to suppose that the antiluetic treatment completed five months before the onset of the edema could be even a partial factor. No remnants of mercury could be found by the *x*-rays at the site of the injections of gray oil.

The patient lost 21 lbs. of weight during two weeks in the hospital but left still markedly edematous. He continued to improve until the middle of November, when his right arm became very swollen and for some days was red and tender. When the edema had somewhat subsided the cephalic vein could be felt as a hard cord under the skin.

On November 1920 he came back even more edematous than before and complaining of dyspnea on exertion and cough. There was fever and leucocytosis but no anemia. After about 500 c.c. of a cell-rich fluid had been withdrawn from the right pleural cavity the temperature became normal and in the next seventeen days 17 lbs. body weight were lost. It was observed that the heart was frequently irregular. The urine still showed the characteristics noted on his first admission.

He was transferred to the City and County Hospital. There the edema gradually decreased but the albuminuria continued. During January 1921 small amounts of sugar were found in the urine, which disappeared when the carbohydrate content of his diet was reduced. Blood pressure readings were taken every few days throughout December 1920 and January and February 1921. The highest pressures were 185 systolic and 100 diastolic and the lowest 165 systolic and 85 diastolic. On February 21 however a reading of 138 systolic and 90 diastolic and a note of a complaint of dyspnea were recorded. On February 16 the blood urea concentration had been reported as 57 mg. per 100 c.c. The systolic pressure continued to fall. On February 24 a condition was present which suggested cardiac dilatation, and he died the next day.

PATHOLOGICAL OBSERVATIONS

At autopsy the heart was found to be twice its normal size. The valves were normal but the coronaries were tortuous and showed a marked thickening. The aorta showed luetic scarring and there was a small aneurysm 2 cm. in diameter in it just above the origin of the superior mesenteric artery.

The left kidney measured 12 × 6 × 4 cm. The capsule stripped easily, leaving a smooth surface, rather pale in color, while the cut surface showed a marked opacity of the cortex. The renal artery was dilated. The right kidney was the same as the left.

Other lesions found were a chronic perisplenitis, hypertrophy of the prostate, cholelithiasis and a general congestion of the viscera.

MICROSCOPICAL EXAMINATION

Glomeruli. The majority of the glomeruli are fairly well preserved; they are of normal size, the tufts are normal and the capsular space clear. In others there is a slight fibrous thickening between the capillary loops of the tufts and a few show a considerable thickening with atrophy of the tuft.

Tubules. The convoluted tubules are very irregular in shape. In the greater part of the cortex they are of normal size, but their epithelium is irregular in size and shape with nuclei often twice normal size. They have all the appearances of immature atypical regenerated cells. Throughout all of these tubules are seen all forms of parenchymatous degeneration, such as cloudy swelling, accumulation of colloid droplets, and fatty degeneration. In some frank necrosis and desquamation is present. The lumens of these tubules are filled with detritus and casts of all sorts with the exception of blood cells or blood casts.

The broad ascending limbs of Henle's loop show the same changes to the same degree. The collecting tubules also contain many casts, but their epithelium is practically normal. No renal failure casts are present.

Interstitial Tissue. There is a moderate diffuse proliferation of the connective tissue throughout the cortex, and in some places definite scar-like areas of fibrous tissue are present. In these regions there is a marked compression and atrophy of the tubules and glomeruli, though the latter, as already stated, are not greatly affected. Throughout the proliferating connective tissue there is everywhere a moderate infiltration with round cells, the process being quite marked in the scars and about the larger arteries.

Arteries. All of the arteries show a moderate fibrous thickening of their intima and about the larger ones there is some perivascular proliferation and leucocytic infiltration.

SUMMARY

The kidneys show very severe epithelial damage, including all forms of degenerative lesions, especially that of fatty degeneration. There is extensive repair by atypical regeneration and a diffuse proliferation of the interstitial tissue. The glomeruli are essentially normal and there is a moderate sclerosis of the arteries.

Case LI

Frank V. Aged twenty-two.

Clinical Diagnosis. Degenerative Bright's disease, cryptic form.

Duration. Edema for seven months before death. Observed during last two months.

Etiology. Unknown.

Course. Edema developed gradually without apparent cause in May 1927. He entered a hospital in the country in June 1927, with extensive edema and a heavy proteinuria. He survived a bronchopneumonia. In spite of energetic treatment the edema persisted. Repeated removal of ascitic fluid was necessary. The blood pressure was normal. A concentration test gave evidence of an intensely degenerative renal lesion without red blood cells. He grew steadily weaker and died on December 3, 1927 after a week of fever.

RELEVANT CLINICAL DETAILS

In May 1927 he found that it was difficult to get his shoes on and observed then that his ankles were swollen. He had no preceding illness and felt quite well. In particular he was sure that there was no dyspnea on exertion, although the swelling was apt to be worse after he had been standing for any length of time, and was less after a night in bed. Not very long afterwards he found that his face was swollen in the mornings and the edema spread up his legs and slowly but steadily increased. By June 21 he was unable to work and on that day he had a severe headache accompanied by vomiting. He was admitted to the San Francisco hospital a few days later. Physical examination failed to disclose any abnormality beyond the extensive anasarca and a heavy proteinuria. A week after admission signs of bronchopneumonia developed but in eight days the temperature was again normal, and his condition was apparently unaltered.

On October 25, 1927 a concentration test was obtained while the patient was still in the San Francisco hospital. The volume was 245 c.c., the specific gravity 1.032. The rate of protein excretion in twelve hours was 4474 mg. The number of casts was 82,000. All of these were hyaline casts sprinkled over with fat droplets and with occasional included cells giving evidence of granular or fatty degeneration. No red blood cells were found. The number of white blood and epithelial cells was 17,200,000 per twelve hours. Many of these were "oval fat body" cells.

At about this time the patient had fluid in both pleural cavities, and a large amount of milky ascitic fluid which reformed rapidly after each removal. There was a soft deeply pitting edema extending to the waist line. The heart was not enlarged, the arteries were not thickened. There was no anemia. The blood pressure was 120 systolic and 85 diastolic. The blood urea concentration was 41 mg. per 100 c.c.

The subsequent clinical course was steadily downward. The edema gradually increased and from October 3 until his death it was necessary to remove 3 or 4 liters of fluid from his abdominal cavity every week. The blood area concentration rose a little until by November 22 it was 62 mg. for 100 c.c. There was then a sudden increase to 124 mg. on November 24. On November 27 the temperature, which had previously been normal, rose to between 100° and 101°F. and remained at that level until his death. The specific gravity of the twenty-four-hour urine collections between November 25 and 28 remained constant between 1.033 and 1.034 with volumes between 450 and 465 c.c. He was then extremely weak. The blood urea concentration on December 3, 1927, the day of his death, was 132 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a terminal bronchopneumonia, a fatty liver and some hematogenous pigmentation of the spleen. An emphysema and healed apical pulmonary tuberculosis were also present. The kidneys were normal in size. Their capsules stripped easily, leaving a smooth greyish purple surface. The cut surface showed a marked opacity of the cortex with indefinite markings. The arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. Except for the presence of granular material in Bowman's space, the glomeruli are normal. There is no increase in their nuclei nor increase in the connective tissue of them.

Tubules. The convoluted tubules and the broad ascending limbs of Henle's loop show all stages and types of degenerative processes. In some there is seen the milder form of cloudy swelling, in others the epithelial cells are greatly swollen and filled with large deeply staining granules. In scattered patches the tubule cells are filled with fine droplets of fat, and in other tubules frank necrosis and desquamation have occurred. The lumens of all the tubules contain granular material, desquamated dead cells, but no red blood cells can be found. In some this material is formed into casts, both hyaline and granular. Regenerative processes are present, as evidenced by the excessive number and large size of the nuclei in some tubules. In the collecting tubules are large hyaline casts, but no typical renal failure casts.

Interstitial Tissue. The interstitial tissue is normal except for a few scattered areas where there is some round cell infiltration and proliferation of connective tissue cells. These areas are very small and are limited to the immediate neighborhood of the arteries.

Arteries. The arteries are normal.

SUMMARY

There are extensive and severe degenerative processes in the epithelium of the cortical tubules. The glomeruli, except for protein leakage, are normal, as are the arteries. The interstitial connective tissue is normal.

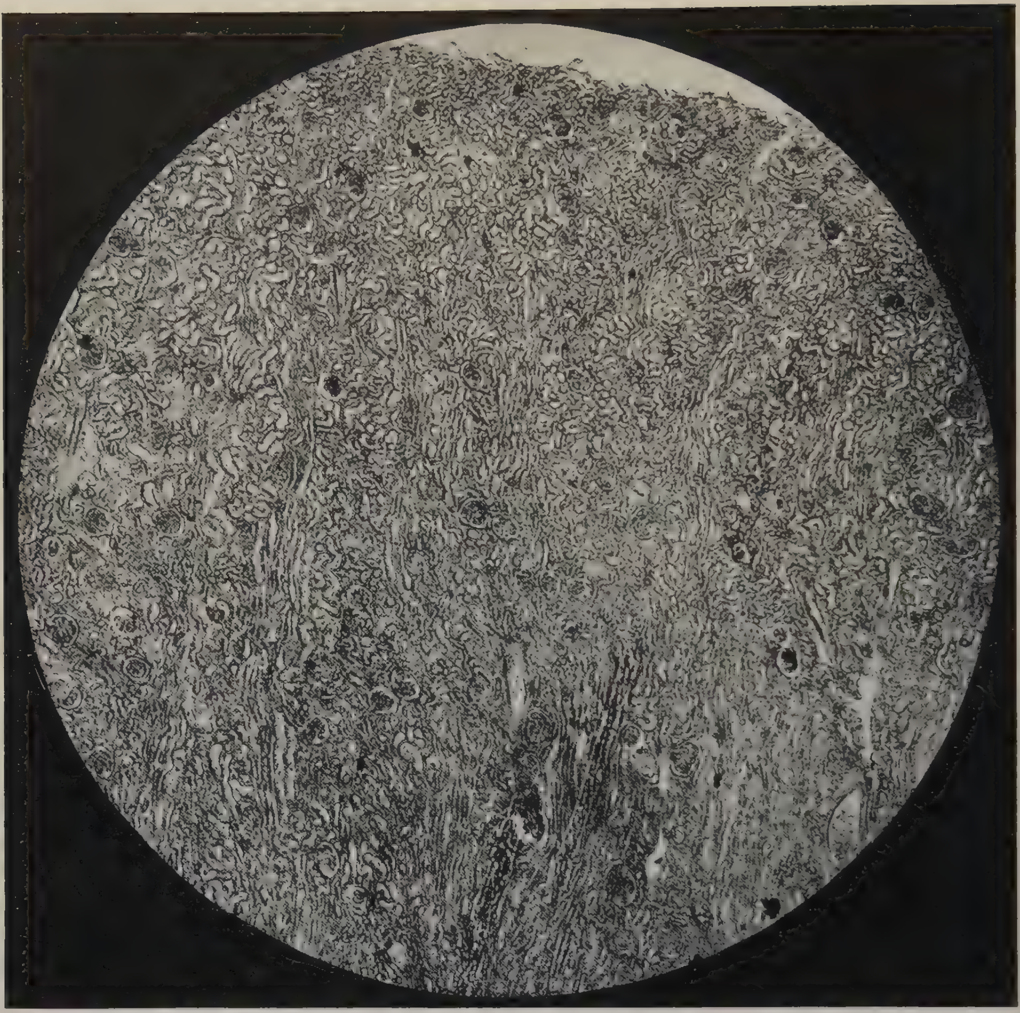

Plate LI a

The marked degeneration of the epithelium of the tubules causes an indefinite and diffuse haziness in the appearance of the section. The glomeruli and vessels are essentially normal. There are some irregular very small areas of connective tissue proliferation and round cell infiltration in the connective tissue framework.

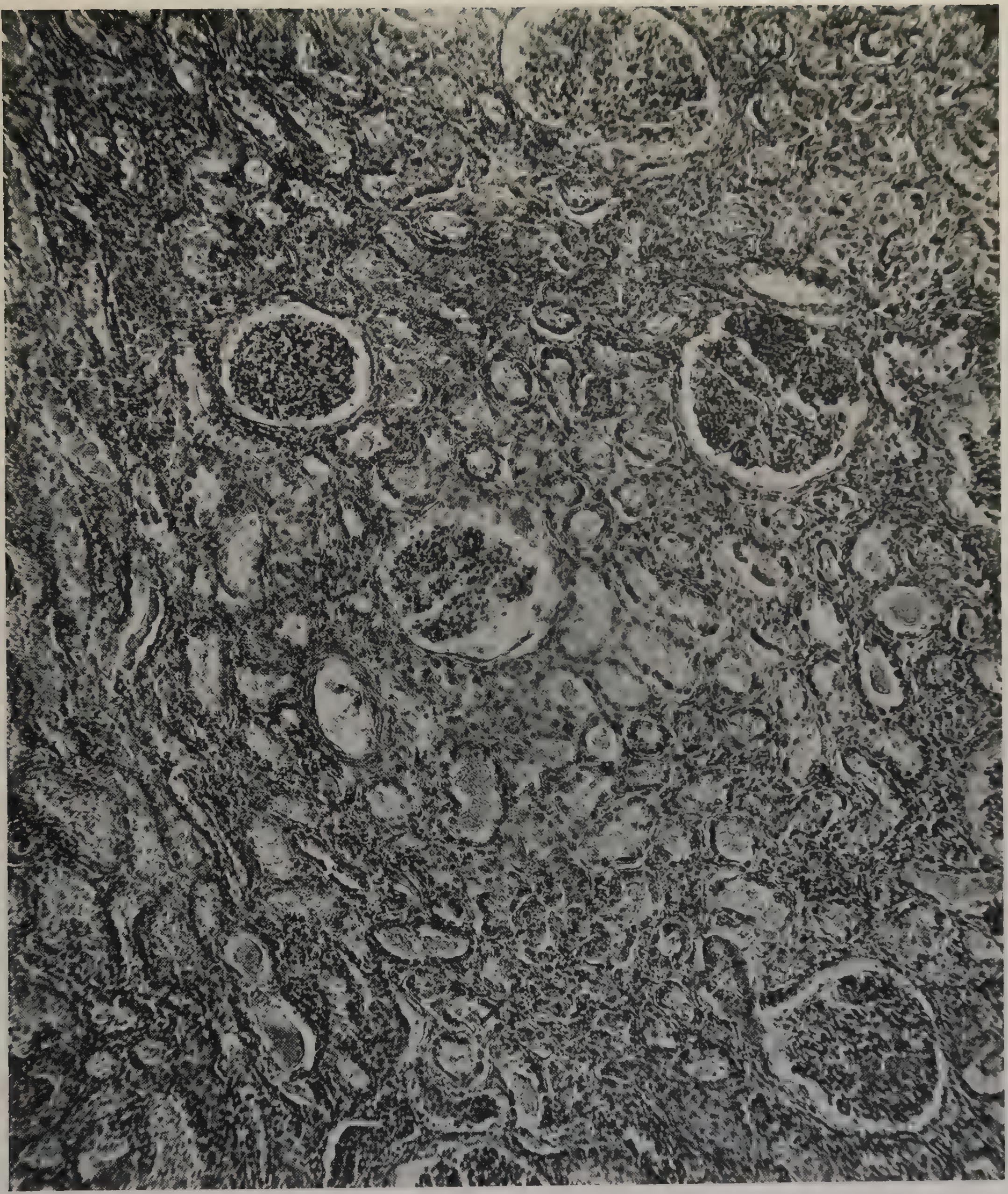

PLATE LI B

There are marked granular degenerative changes in the tubular epithelium and the lumens of the tubules are filled with casts and debris. The glomeruli and interstitial tissue are essentially normal.

THE PYOGENIC FORM

CASE LII

Benjamin C. Aged ten.

Clinical Diagnosis. Degenerative Bright's disease, pyogenic form.

Duration. Unknown, but more than one year. Observed during the last three months.

Etiology. Tuberculous osteomyelitis of the spine with secondary infection and continuous suppuration.

Course. In 1926 the patient was under treatment for tuberculosis of the spine. He entered the hospital in September 1927 with a draining sinus, markedly emaciated and with ascites. Edema became pronounced. The blood pressure was very low. During October and December the urinary sediment showed evidences of degeneration without any marked increase in red blood cell excretion. The boy became more edematous and died on December 8, 1927 after a severe diarrhea had commenced.

RELEVANT CLINICAL DETAILS

When the patient entered the hospital in September 1927 there was a sinus, draining thick yellow fluid, opening in the lower part of the neck. It was not ascertained for how long this suppuration had continued. There was marked kyphosis and evidence in the *x*-ray of tuberculosis of the third, fourth and fifth cervical and first, second and third dorsal vertebrae. There was slight generalized edema, with a moderate ascites, no anemia. Blood pressure was low. A concentration test on October 25 gave a volume of 220 c.c. in twelve hours with a specific gravity of 1.019. There were 1,180,000 casts, no red blood cells, and 4,400,000 white blood cells and epithelial cells. The urea concentration in some ascitic fluid which was withdrawn was only 12 mg. per 100 c.c.

It was not possible to get the child to eat enough and the edema slowly increased. Repeated removal of abdominal fluid was necessary. There was daily a marked fever. On December 5 in a timed collection of urine 925,000 casts per twelve hours were estimated, with 940,000 red blood cells, and 4,040,000 white blood cells and epithelial cells. The boy was now very weak, and he died on December 8, 1928, a few days after the onset of a severe diarrhea. It is clear from the nature of the urinary sediment, which contained no renal failure casts, that there was no uremia.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found an active chronic pulmonary tuberculosis with secondary involvement of the intestines, mesenteric lymph glands and the cervical and thoracic vertebrae. Amyloid disease involved the liver, kidneys, spleen and intestinal and gastric mucosa.

The kidneys were of normal size. Their capsules stripped easily, leaving a smooth greyish pink surface. The cut surface showed an opacity of the cortex. The pelvis of the kidneys and the arteries were normal.

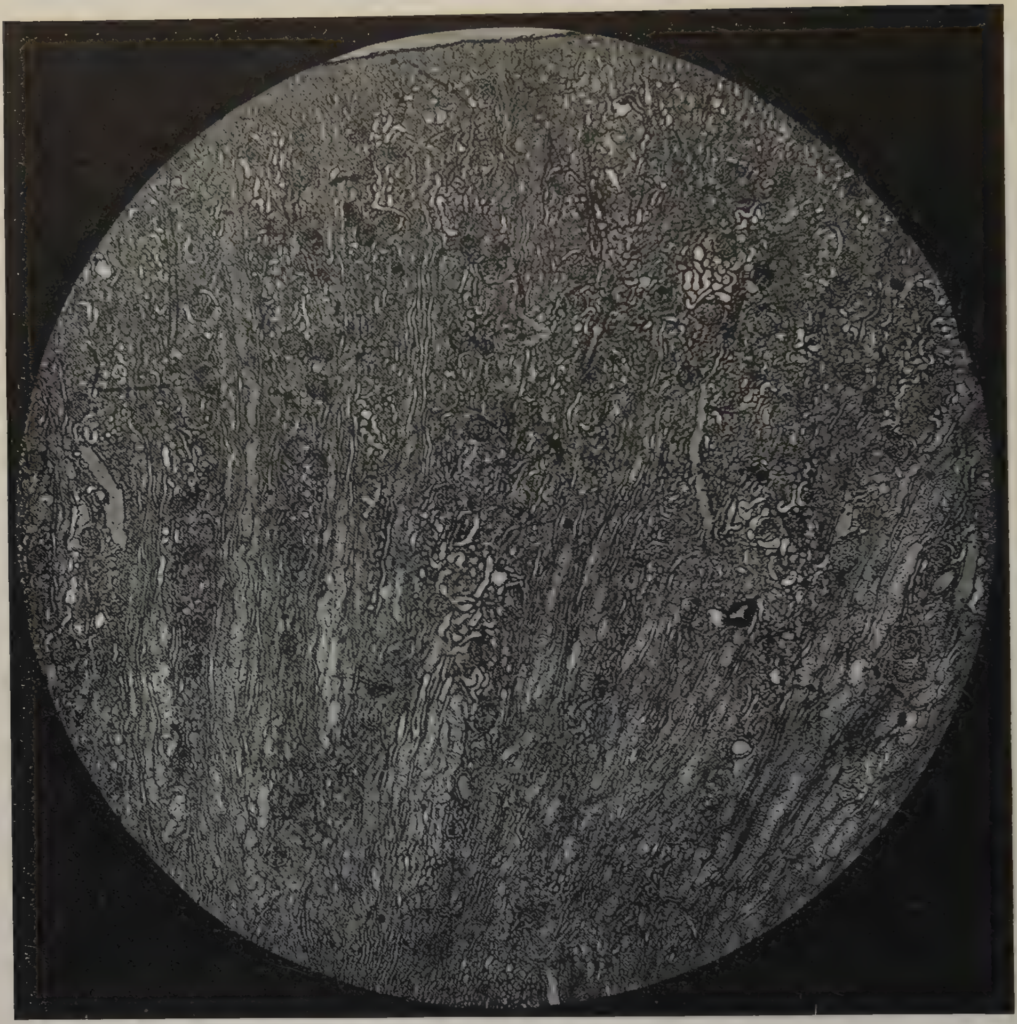

PLATE LII A

The marked epithelial degenerative changes in the swollen, light staining tubules in the lower levels of the cortex are plainly seen. (Cf. Plate LXXIII.) The amyloid deposits in the glomeruli are too small to appear at this magnification. The interstitial tissue and vessels appear normal.

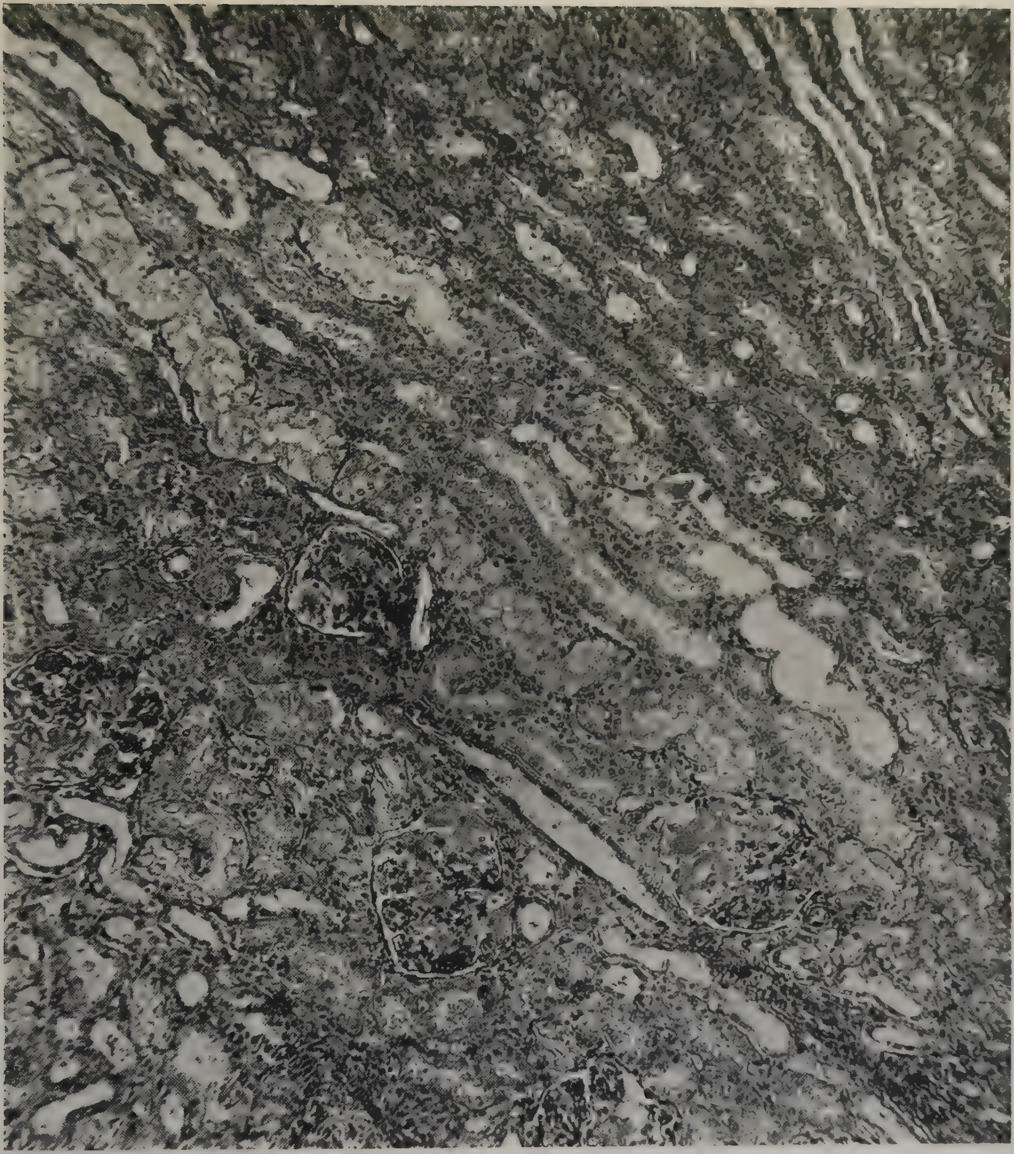

PLATE LII B

In the glomeruli may be seen small deposits of amyloid. Running diagonally through the figure is the terminal portion of a convoluted tubule whose epithelial cells show the coarsely granular form of cloudy swelling. In the remaining convoluted tubules the cloudy swelling is of the more commonly seen fine granular type. (Cf. Plate LXXIII.)

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus examined shows a deposit of amyloid in the tuft. In the majority of them the masses are quite small and limited to two or three clumps. In others about a third of the tuft is obliterated, and very rarely does the amyloid occupy more than half of the glomerulus. The deposit may be followed from the afferent vessel, which stands out prominently because of the infiltration about its wall, along and into the capillaries of the tuft. The uninvolved portions of the tuft are essentially normal. The capillaries are patent and there is no leucocytic infiltration nor fibrosis. Bowman's space is free of exudate and granular material.

Tubules. The convoluted tubules of the cortex and broad ascending limbs of Henle's loop show extreme degenerative processes. Fatty degeneration is seen in scattered small focal areas, but cloudy swelling is the process most frequently observed. The cells of the tubules are greatly swollen and filled with large deep eosinophilic granules. As a rule the nuclei are intact in these cells; occasionally there is necrosis and desquamation. The lumens are filled with coagulated hyaline and granular material which in the straight tubules is organized to definite casts. No renal failure casts are present.

Interstitial Tissue. The interstitial tissue is essentially normal. An occasional small group of round cells can be found around some of the larger arteries.

Arteries. The larger arteries are normal. Around the arterioles to the glomeruli and the capillaries of the vasa recta is a thin deposit of amyloid.

SUMMARY

The kidney shows a moderate deposit of amyloid around the capillaries and arterioles of the glomeruli and medulla. There are severe degenerative changes in the epithelial cells of the cortical tubules. The interstitial tissue and large arteries are normal.

CASE LIII

Henry C. Aged forty-two.

Clinical Diagnosis. (1) Degenerative Bright's disease, pyogenic form. (2) Renal arteriosclerosis.

Duration. Unknown.

Etiology. Tuberculous osteomyelitis with secondary infection through the sinus.

Course. The patient had had a discharging sinus below the left knee for some years. He was seen on one occasion in December 1921. He stated that a year previous there had been for a short time a swelling of the face and legs. His immediate complaint was severe headache. At this time there was no edema. The heart was enlarged to the left, the systolic pressure 200 and the diastolic 130. There were recent retinal hemorrhages. The urine contained a large amount of protein. There was a gross pyuria. Only a few hyaline casts were found. The blood urea concentration was 63 mg. per 100 c.c.

He was not seen again until August 1922, a day before his death. There was an extensive anasarca. The blood urea concentration was over 200 mg. per 100 c.c. No urine was obtained. The long-continued suppuration associated with a very marked proteinuria made it seem likely that amyloid and a degenerative lesion would be found in the kidney. That hypertension should be present in such a state led to the conclusion that the degenerative process had involved an organ already atrophied by arteriosclerosis.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained at autopsy. They were somewhat under normal size, measuring 10 × 4 × 3 cm. Their capsules stripped with some difficulty, leaving a rather rough pinkish grey mottled surface. The cut surface was very opaque and the normal markings obscured. The arteries were somewhat rigid.

MICROSCOPICAL EXAMINATION

Glomeruli. Every glomerulus is heavily infiltrated with amyloid. This substance in most cases forms a solid mass in which a few atrophied cells and compressed capillaries lie. In most the hyaline material is pure amyloid, but in some there is also a formation of considerable collagen and in the remaining tissues of the tuft is leucocytic infiltration with round cells and a few polymorphonuclears. Bowman's space is as a rule reduced by the swelling of the tuft which has resulted from this infiltration but is free of fibrinous exudate or granular material.

Tubules. The whole architecture of the cortex has been altered by the proliferative and infiltrative changes in the interstitial tissue. Most of the tubules are collapsed and distorted and their epithelium atrophied and atypical. In many tubules proliferative changes of a regenerative nature have increased the size and number of the cells so that they form giant cell-like masses more or less obliterating

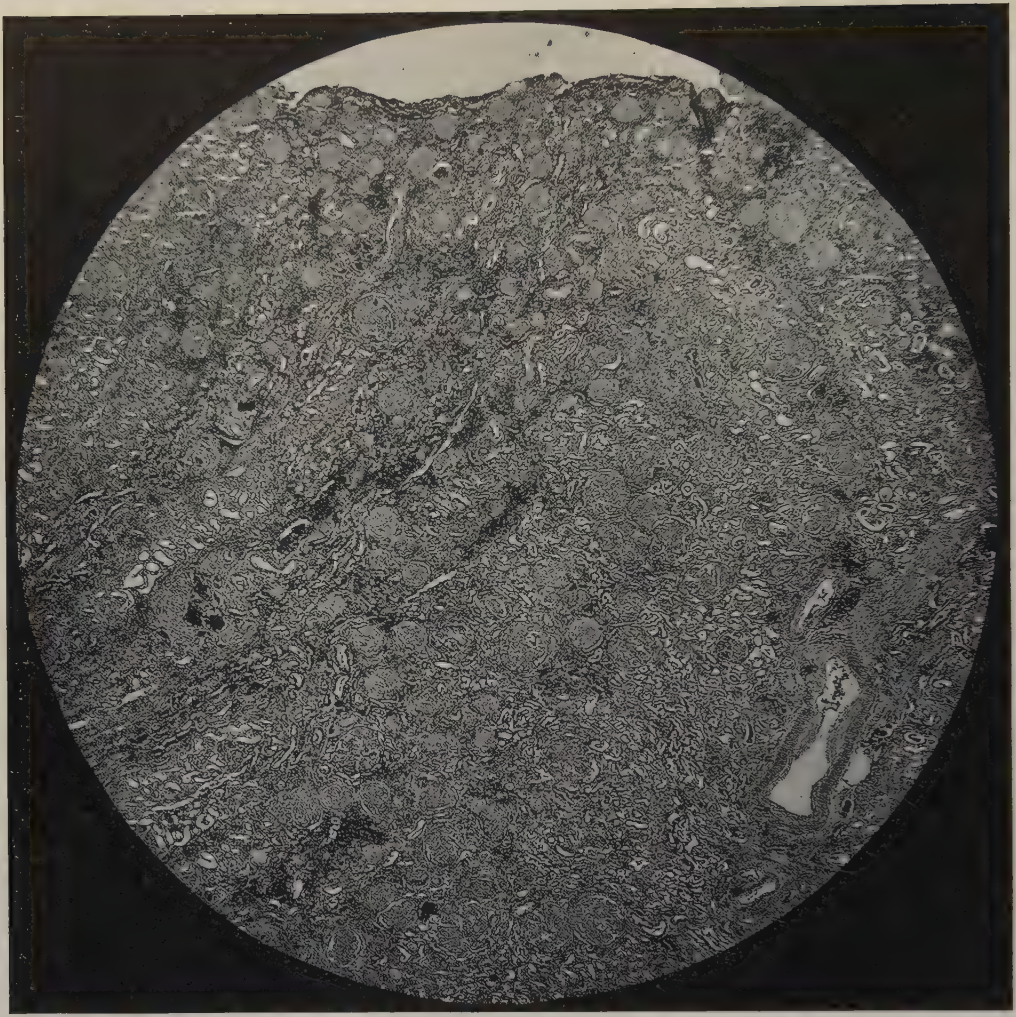

Plate LIII a

The huge glomeruli heavily infiltrated with amyloid are seen scattered through the cortex. The interstitial tissue is markedly thickened and shows scattered irregular dark areas of leucocytic infiltration. As a result the tubules are either compressed and atrophied or dilated and filled with colloid. There is also a marked fibrous thickening of the arteries.

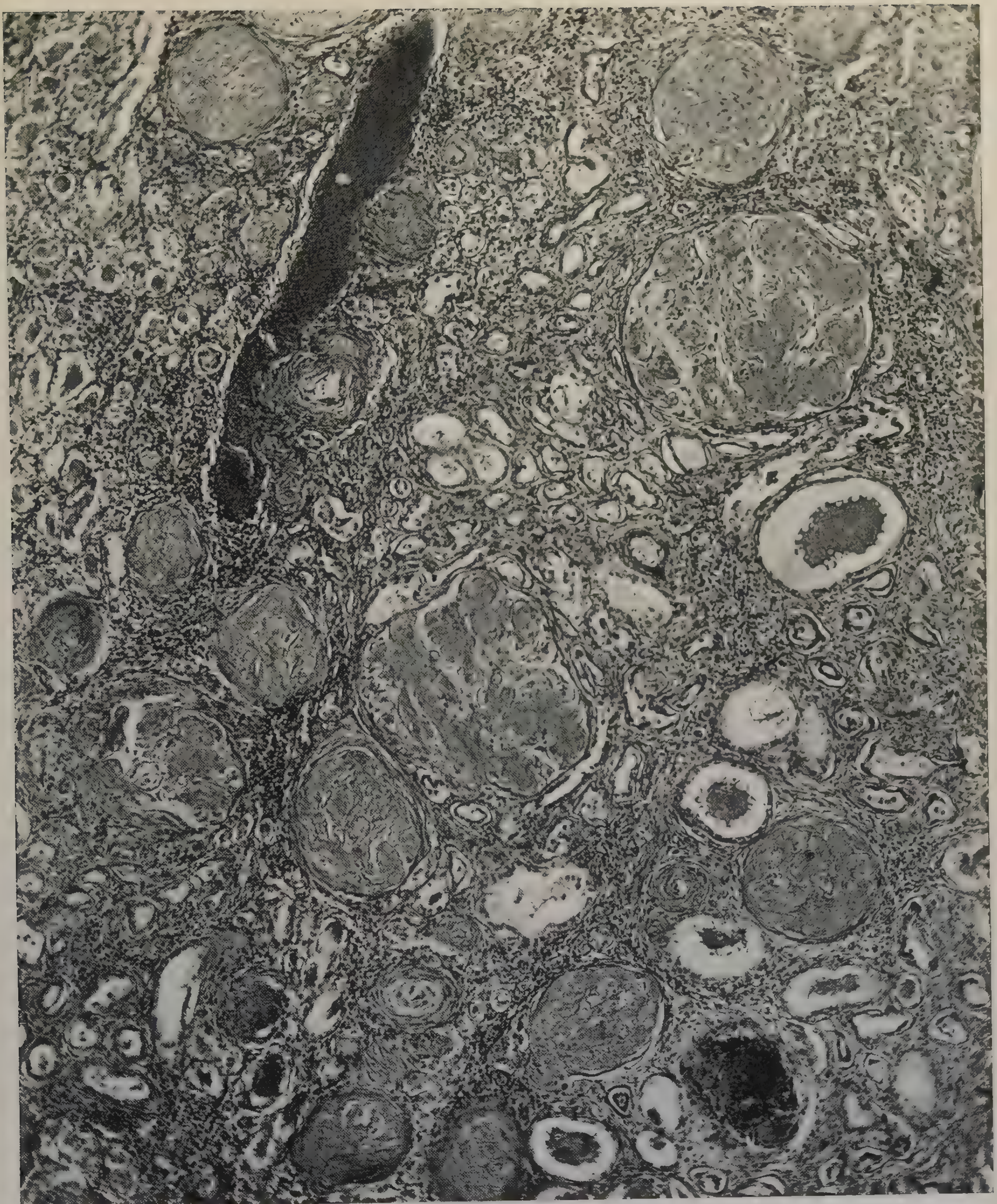

Plate LIII b

All of the glomeruli are filled with masses of amyloid. Throughout the interstitial tissue is seen a heavy round cell infiltration and development of connective tissue which compresses and distorts the tubules. Many casts are present in the latter.

the tubule lumen. Other tubules are greatly dilated, their epithelium is compressed and their lumens are filled with colloid material. There is some cloudy swelling and some fatty degeneration in the cells of the convoluted tubules and broad ascending limbs of Henle's loop, but neither to an extreme degree. The lumens of the tubules contain granular and hyaline material, desquamated cells and casts of all sorts. Some tubules contain many leucocytes, mostly of polymorphonuclear type. No blood cells or blood casts however are found, nor are large renal failure casts present in the collecting tubules.

Interstitial Tissue. There is a very marked fibrous proliferation of the interstitial tissue throughout the cortex with obliteration and distortion of tubules and glomeruli. The new-formed tissue is quite fibrous and is heavily infiltrated with leucocytes. These are chiefly mononuclears but many polymorphonuclears are also present.

Arteries. There is an infiltration with amyloid around the smaller arteries of the cortex and around the vasa recta of the medulla. The larger arteries show a marked fibrous thickening of their intima and the smaller branches to the cortex are also thickened.

SUMMARY

There is an extreme infiltration in the glomeruli and around the vasa recta with amyloid. The tubular epithelium shows degenerative processes and there are very marked and very active proliferative inflammatory processes in the interstitial tissue. The arteries are sclerotic.

CASE LIV

Leonard C. Aged thirty-one.

Clinical Diagnosis. Degenerative Bright's disease, pyogenic form.

Duration. Three years. Observed during the last year.

Etiology. Continuous suppuration for three years associated with bone infection.

Course. In the autumn of 1918 an abscess was opened near his shoulder joint. Sinuses formed and in spite of many operations there was a continuous drainage of pus until his death. In January 1920 he began to lose strength. The urine was found to contain a small amount of albumin. A few weeks later his legs became edematous and large amounts of albumin were found in the urine. In August of that year the blood urea concentration was 34 mg. per 100 c.c. There was no hypertension but the albuminuria and the edema had persisted. In January 1921 the urinary sediment indicated the presence of an active degenerative process in the kidney. He was not seen again until shortly before his death in January 1922. He had grown progressively weaker with increasing edema of the legs and latterly there had been a large accumulation of fluid in the abdominal and pleural cavities. The urinary sediment contained many fatty casts and some renal failure casts. He died of pulmonary edema.

RELEVANT CLINICAL DETAILS

In October 1918 his shoulder was accidentally bruised. In spite of rest the swelling did not subside, but became more and more painful. After six weeks an abscess was opened which led down to bare bone. A sinus formed and in spite of a resection of the shoulder joint and several other operations pus continued to drain from one sinus or another up to the time of his death more than three years later.

His general health remained fairly good until January 1920 when his appetite failed and he felt weak and listless. He remembered that about this time a small amount of albumin was found in the urine. A few weeks later he found that his ankles were swollen and at that time a considerable amount of albumin was discovered in the urine. Throughout this period he had made observations on he appearance of the urine and is certain that it was always a clear amber color and never an opaque brown or red.

In August 1920 he was referred to a doctor for examination. At that time there was definite edema in both legs, the liver was palpable, the blood pressure was 134 systolic and 78 diastolic, and the blood urea concentration was 34 mg. per 100 c.c. The urine contained much albumin and many casts.

He was seen first in January 1921. His face was puffy, and pitting edema extended to the knees. The blood pressure was 130 systolic and 85 diastolic. The concentration test gave a volume of 564 c.c. and a specific gravity of 1.023. The rate of protein excretion was 8500 mg. per twelve hours. The number of casts was 237,000 in twelve hours. Of these 13 per cent were classed as epithelial, 21 per cent as granular and 66 per cent as hyaline. Most of the casts contained fat droplets.

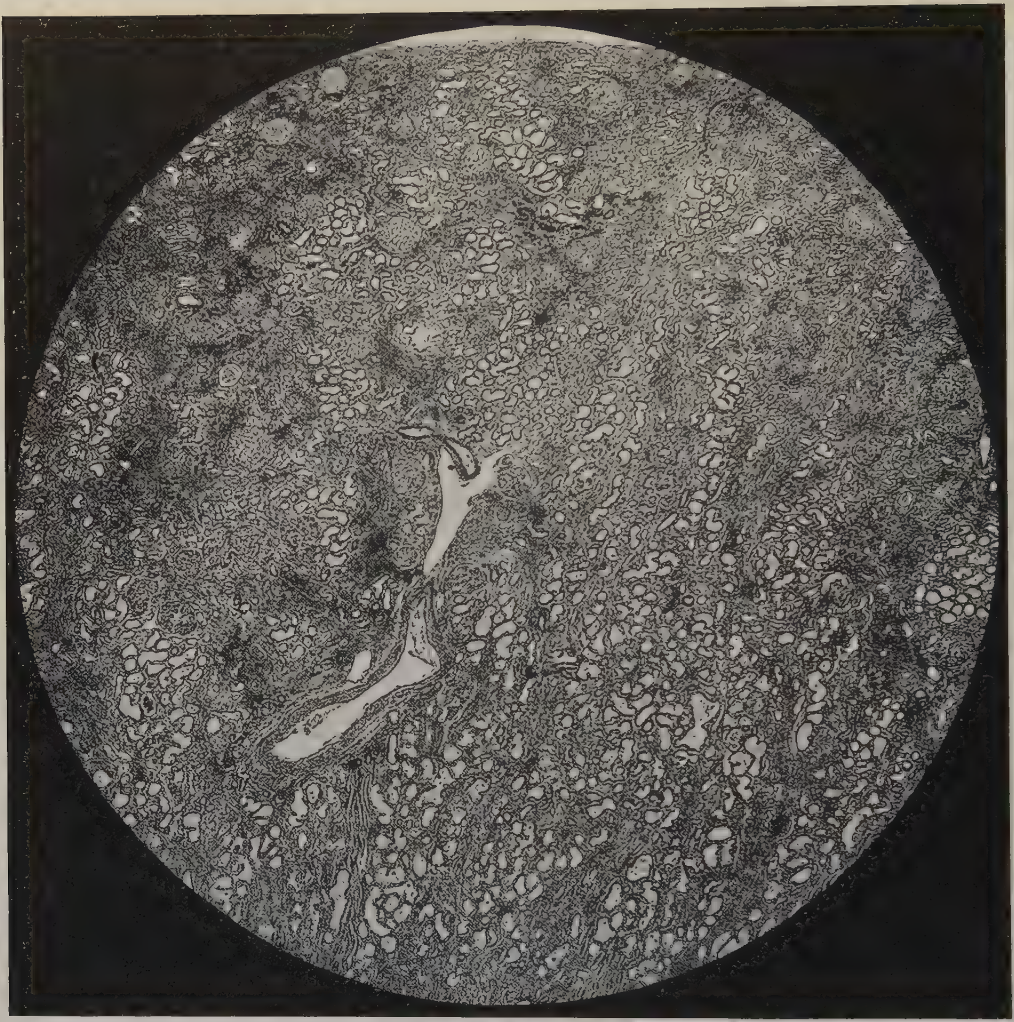

Plate LIV a

The glomeruli appear as light indefinite areas due to the infiltration of them with amyloid. There is an extensive profuse proliferation of the connective tissue with irregular areas of heavy round cell infiltration. The tubules are collapsed or dilated and the arteries show a moderate sclerosis.

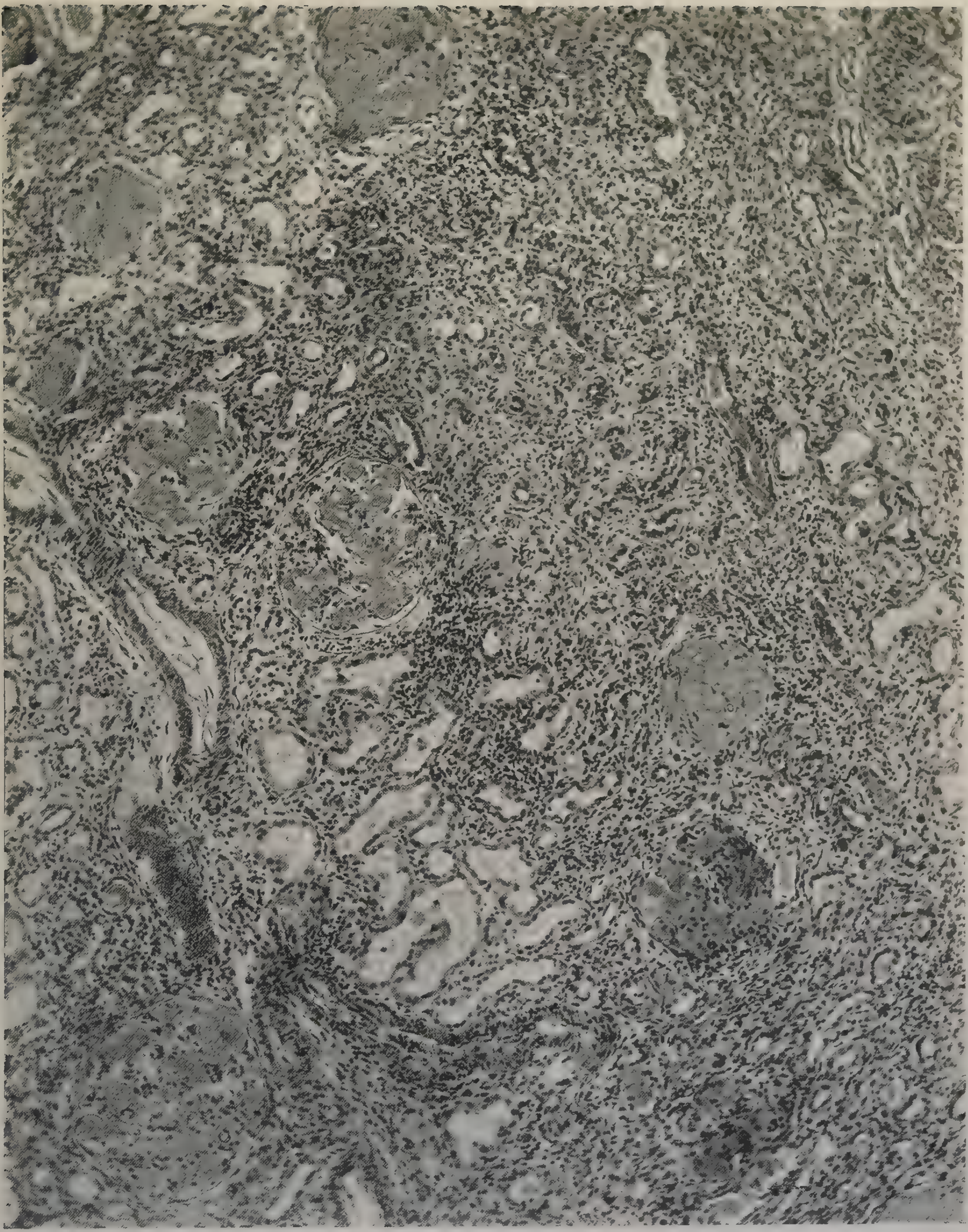

PLATE LIV B

The inflammatory proliferation and leucocytic infiltration of the interstitial tissue is marked. The tubules are distorted and their epithelium shows various degenerative changes. The glomeruli are heavily infiltrated with amyloid.

The phenolsulphonephthalein excretion was 58 per cent in two hours and ten minutes. When urea and large amounts of water were given there was no diuresis, so it was not possible to determine the amount of functioning renal tissue. At that time it was concluded from the practical absence of red blood cells and from the nature of the urinary sediment that no inflammatory but an active degenerative process was present in the kidneys.

He was not seen again until January 1922. During 1921 his strength had steadily failed. There was very marked general anasarca and signs of fluid in the abdominal and pleural cavities. The urinary sediment was changed in respect to the addition of a certain percentage of renal failure casts, but it still contained a high percentage of epithelial, granular and fatty casts. Death appeared to be due to pulmonary edema.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found an old discharging sinus in the left shoulder. Collections of clear fluid were present in the abdominal and pleural cavities. The heart was normal in size and the valves were normal. The spleen showed no gross abnormalities but the liver though not enlarged was distinctly greasy on its surface.

The left kidney measured 13 × 6 × 4 cm. The capsule stripped easily, leaving a slightly granular surface of pale yellow color with irregular areas of congestion. The cut surface showed a distinct widening of the cortex with the same yellowish coloration as seen on the external surface. The medulla and pelvis were apparently normal, as was the renal artery. The right kidney was the same as the left.

No other significant lesions were found in any of the other organs.

MICROSCOPICAL EXAMINATION

Sections of liver and spleen show large deposits of amyloid.

Kidneys. *Glomeruli.* Practically all the glomeruli are enlarged and show heavy deposits of amyloid but in the great majority in spite of the compression and atrophy of the tuft there are a few capillary loops present which are still patent. This deposit of amyloid is the only significant lesion in the glomeruli, as there is no fibrosis of them nor any collections of an inflammatory exudate of fibrin or leucocytes.

Tubules. There is a marked irregularity in the size and shape of the convoluted tubules. In the areas of denser fibrosis they are collapsed and lined with an atrophic epithelium, while in the other areas they are much larger than normal and lined with high swollen epithelial cells. Scattered throughout are many tubules which are lined with irregular cells sometimes in several layers. These contain excess nuclei or mitotic figures as evidences of regenerative repair. The epithelial cells also present extreme degenerative changes. These take the form of cloudy swelling, colloid droplet degeneration, fatty degeneration and in places necrosis. The lumens of the tubules are filled with detritus, or hyaline and granular casts. No blood cells or blood casts are present. The broad ascending limbs of Henle's loop show the same changes. The collecting tubules contain many casts, but their epithelium is well preserved.

Interstitial Tissue. There is a diffuse proliferation of the connective tissue throughout the cortex, and to a lesser degree in the medulla. In scattered areas the proliferation is more dense, and definite scars are formed, and here the atrophy of the convoluted tubules previously mentioned is marked. Throughout all this new-formed connective tissue is a heavy infiltration with leucocytes. The majority of these cells are lymphocytes, though a few scattered polymorphonuclears may be found.

Arteries. There is a slight increase in the connective tissue of the intima of the larger arteries, but the proliferation is not marked in any of them.

SUMMARY

Amyloid infiltration of the kidney is combined with marked parenchymatous degeneration, necrosis and regeneration of the tubular epithelium. There is also present a productive inflammatory process in the interstitial tissue, though no inflammatory lesions are noted in the glomeruli. The arteries are practically normal.

CASE LV

William H.

Clinical Diagnosis. Degenerative Bright's disease, pyogenic form.

Duration. Evidence of the existence of a renal lesion was obtained eight years before death. Observed for the last four years.

Etiology. Suppuration for twenty-three years. Osteomyelitis.

Course. In 1903, as a result of osteomyelitis, several sinuses developed which drained pus at intervals until his death. In 1918, albumin was found in large amount in the urine and in 1920 he became edematous. In 1922, when first seen, the blood urea concentration was above normal. The sediment showed an excess of epithelial cells, few or no red blood cells, and as the blood urea concentration gradually rose, an increasing number of renal failure casts. Edema in varying degree was always present. During the last year, there was an extreme anemia. He died in 1926.

RELEVANT CLINICAL DETAILS

In 1903 during convalescence from smallpox, he lacerated his right thigh against a sharp rock while he was diving into a pool. The wound became infected and he was in bed for months with a high fever and much pain in his hip joint. The condition was finally diagnosed as tuberculous, and the joint was resected. Although the operation wound healed, several sinuses formed from which there was intermittent drainage during the next two or three years.

From 1903 to 1918, he was able to work for the greater part of the time, but suffered from repeated suppurations in various parts of the body. They were all superficial and healed after they had been opened, but the drainage of pus from one or other of the sinuses around his hip joint continued with only short intermissions.

In 1918, albumin was found for the first time in the urine. He had had a fever and pain in the abdomen with signs which suggested appendicitis. He was to have been operated on but the routine urine examination showed such a large amount of albumin that the operation was postponed. He remembers that one specimen contained 2.2 per cent of protein as estimated by Esbach's method. The phenolsulphonephthalein excretion was within normal limits. The blood pressure was said to be normal. It was found that his liver was much enlarged and he recollected that he could readily palpate the edge well below the costal margin. Although he was told that there was no pus in the urine the ureters were catheterized. He was later informed that tests indicated that he did not have tuberculous disease of the kidneys. From this time onwards, he was definitely weaker and less able to work. He suffered particularly from dyspeptic symptoms, and at times from diarrhea. In 1919, his appendix, his tonsils, and all but five of his teeth were removed.

In 1920, he first noticed a swelling of his ankles, especially marked on the side of the resected joint. The edema was at times noticeable in his face. The swelling in the legs was always least in the mornings, but never entirely disappeared. He was told that the albuminuria continued to be very pronounced, but several blood pressure determinations were all within the limits of normal variation.

In February 1922, he was seen for the first time. His main complaint was weakness and loss of weight. There was a moderate edema of both legs to the knees. The liver could not be felt, nor could the spleen be palpated. The heart was apparently not enlarged, though there was a loud systolic murmur transmitted into the axilla. No thickening of the arteries could be detected. The systolic blood pressure was 120 and the diastolic 85. The red blood cells numbered 3,500,000 per cubic millimeter. The volume of the concentration test was 1125 c.c. for twelve hours, with a specific gravity of 1.014. The rate of protein excretion was 16,500 mg. per twelve hours. The number of casts was not large, but it is probable that many of the hyaline casts had been dissolved. There were no renal failure casts seen. Six per cent of the casts were waxy and the remainder hyaline. The blood urea concentration was 78 mg. per 100 c.c. The ratio test showed that only 15 per cent of the normal amount of renal tissue was still functioning, but since the largest hourly volume of urine obtained during the test was only 140 c.c. the conditions for quantitative accuracy were not fully met.

In August 1922 the rate of protein excretion was 8700 mg. per twelve hours. The ratio test showed only 9 per cent of function, but it was impossible to induce diuresis. The blood urea concentration had risen to 110 mg. per 100 c.c.

In March 1923, there was no great change in his clinical condition, but the blood urea concentration was 143 mg. per 100 c.c. The concentration test had a volume of 1080 c.c. per twelve hours with a specific gravity of 1.015. The rate of protein excretion was 8160 mg. per twelve hours. No red cells could be found in the urine. In August of that year the urine was still dilute, but the protein excretion had fallen to 3970 mg. per twelve hours. In January 1924, it was 3680 mg. per twelve hours.

In August 1924 he was admitted to the hospital because the anemia which had been noted in 1922 was now much more pronounced. The red blood cells had fallen to 2,300,000 per cubic millimeter. No sufficiently accurate hemoglobin determination was made, but the anemia had all the characteristics of the secondary type. At the time an electrocardiogram showed a definite left ventricular preponderance and the systolic blood pressure was 142 with the diastolic 84. It was thought that the edge of the liver could be felt just below the costal margin, but the spleen could not be palpated. It was reported that the retinal arteries were perhaps slightly tortuous, but that otherwise no lesions could be seen. There was edema of the legs, but no fluid in the abdominal or pleural cavities. The blood urea concentration had fallen to 113 mg. per 100 c.c. The rate of protein excretion was 3680 mg. per twelve hours. The volume of the concentration test was 890 c.c. with a specific gravity of 1.015. He was kept in bed for nearly a month and during this time the rate of protein excretion fell as low as 1100 mg. per twelve hours, but the blood urea concentration rose to 144 mg. per 100 c.c. The number of casts was never large. In the most concentrated collection made 318,000 per twelve hours

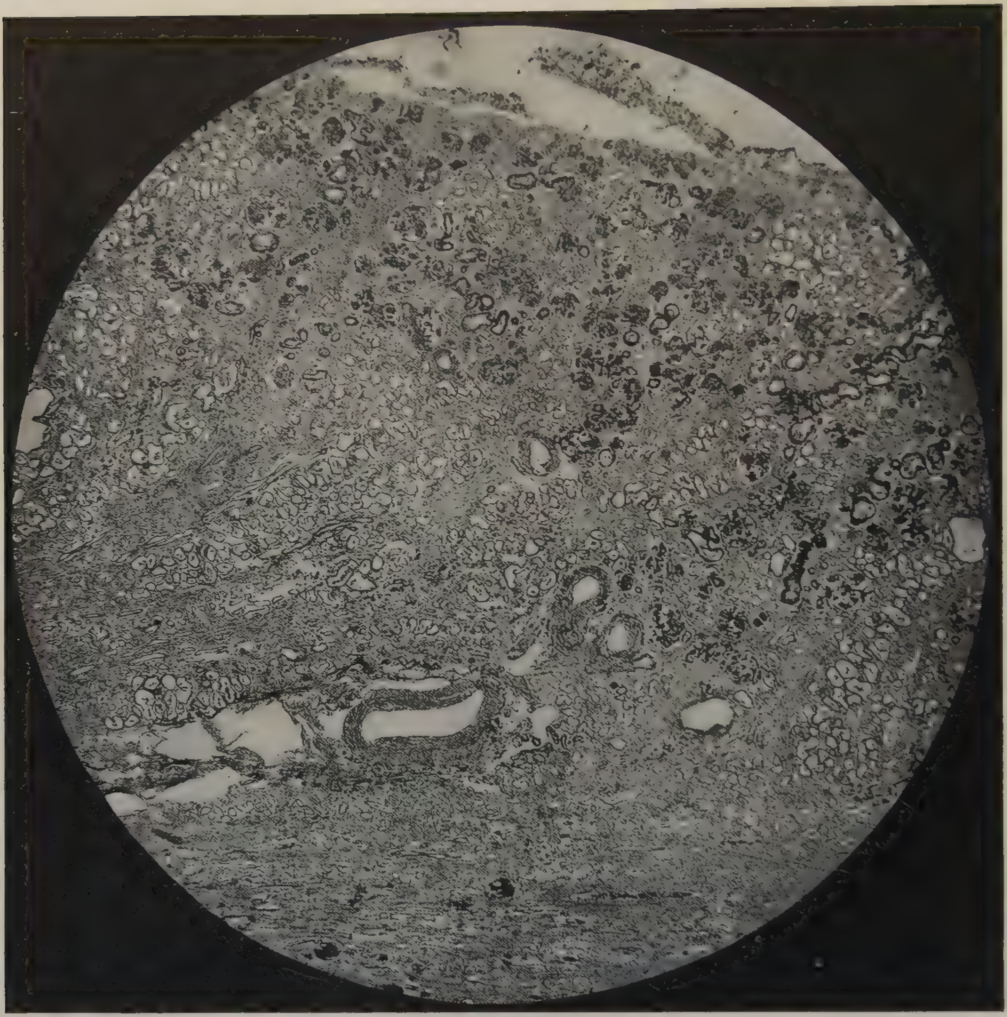

Plate LV a

In this section the amyloid appears as if stained black. Throughout the cortex all the glomeruli are heavily infiltrated with this substance and deposits may also be seen around the small arteries. It is also evident in the medulla along the straight vessels in the right part of the figure. There is extensive connective tissue proliferation in the framework of the kidney with resulting collapse or dilatation of the tubules. The arteries show a moderate fibrous thickening.

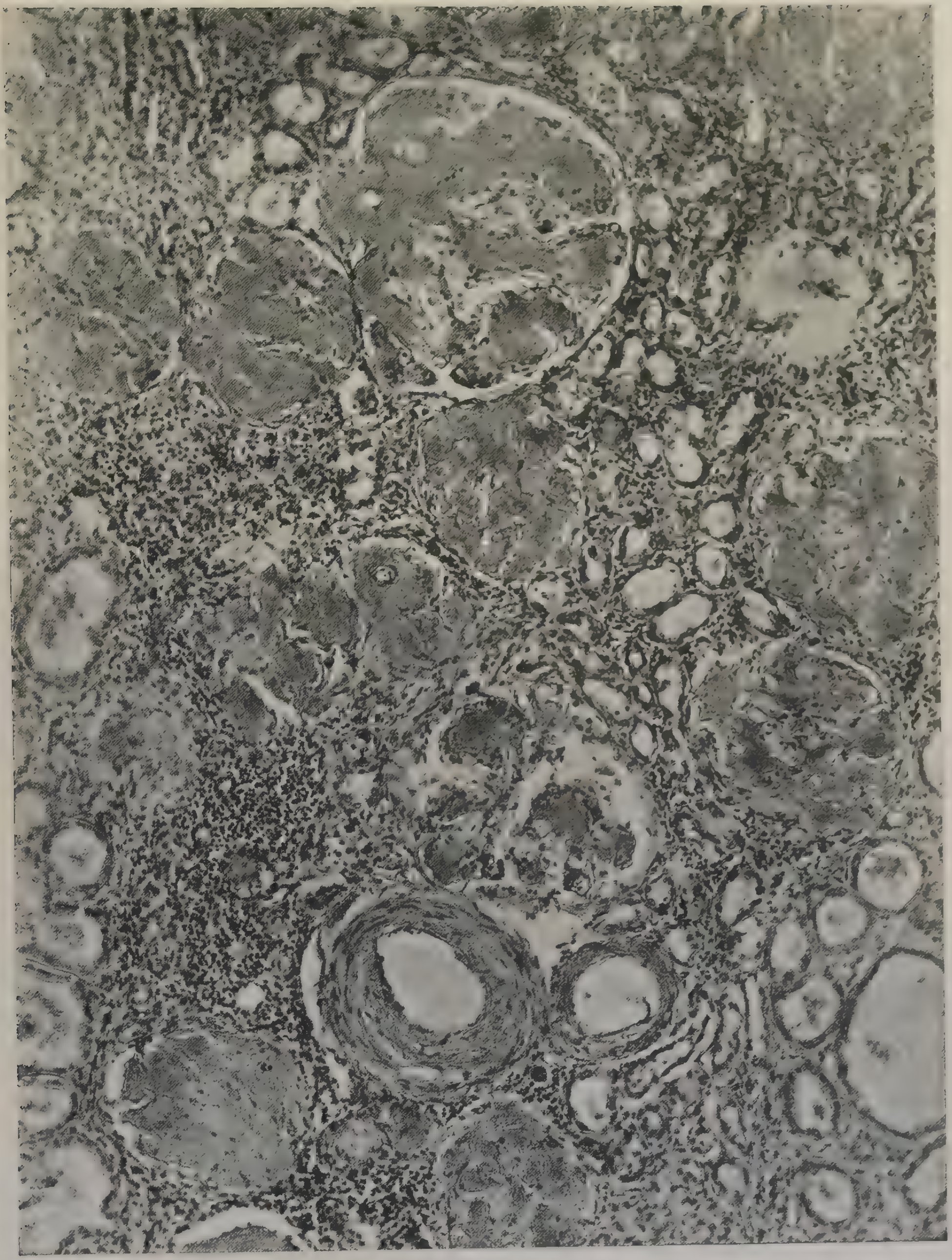

PLATE LV B

The glomerular tufts are almost replaced by masses of amyloid. In the interstitial tissue are seen the inflammatory processes of leucocytic infiltration and connective tissue proliferation. Two sclerotic arteries are seen at the bottom of the section. (Cf. Plate LXXIX.)

was counted. A considerable percentage of these casts were now of the renal failure type. In one twelve hour collection 247,000 red blood cells were found. The number of white blood cells and epithelial cells in the same urine was 1,350,000.

He was given 500 c.c. of blood shortly before his discharge from the hospital, and left superficially much improved.

From September 1925 until his death in March 1926 no direct observations could be made as he lived in southern California, but he was often heard from by letter. Dr. Sherrill at San Diego was kind enough to send some observations among which the most interesting were blood pressure readings made on several occasions during 1925 which indicated that he had developed a moderate but definite hypertension, the systolic varying between 140 and 168 and the diastolic from 85 to 104. There was still a heavy albuminuria, edema of the legs, and a marked anemia.

In January 1925 phenolsulphonephthalein excretions of 5 per cent and 1.5 per cent were obtained.

In March 1926 Dr. F. E. Smith of Los Angeles wrote that he had been called to see the patient. He was suffering from "marked weakness and severe dyspnea. His breathing impressed one as being an air hunger rather than a dyspnea of cardiac origin." The red cells numbered 1,200,000 per cubic millimeter. A transfusion was recommended but refused and he died a few days later. Dr. Smith obtained permission for an autopsy, and Dr. Hammock who performed it very kindly sent us parts of the liver, kidneys and spleen.

PATHOLOGICAL OBSERVATIONS

A portion of the liver, the spleen and the kidneys only were obtained for examination.

The cut surface of the portion of liver appeared normal. The spleen was large, measuring 23 × 10 × 16 cm. and its cut surface showed grossly an amyloid infiltration.

The kidneys were identical in appearance. They were small, measuring 9 × 5 × 3 cm. The capsule was rather adherent as it stripped with difficulty leaving a fine granular surface which was a yellowish grey color. The cut surface showed a definite decrease in the breadth of the cortex and the markings were indistinct. The renal arteries were somewhat thickened.

MICROSCOPICAL EXAMINATION

Sections of both liver and spleen show an infiltration with amyloid.

KIDNEYS. *Glomeruli.* A search through many sections fails to show a glomerulus which has maintained its normal structure. All are filled with large masses of amyloid which have severely compressed the capillary loops of the tufts and produced an almost complete atrophy of them. All that remains of the blood vessels in the tuft are remnants of shrunken flattened cells, many of which show a fatty degeneration. The tufts are therefore bloodless and the capsular spaces obliterated. There is a slight periglomerular fibrous thickening about some of the glomeruli, but none within the tuft proper.

Tubules. A considerable number of the convoluted tubules are compressed by the newly developed connective tissue which infiltrates the cortex. They consist of shrunken tubes with distorted lumens and in some places of solid cords of atrophic dark staining cells. The epithelium in many of these shows a fatty degeneration. In those regions of the cortex which are comparatively free of connective tissue proliferation the convoluted tubules are larger than normal and their epithelium distinctly hypertrophied. Many of them are dilated. The epithelium shows all varieties and degrees of degeneration, such as cloudy swelling, colloid droplets accumulation, fatty degeneration and necrosis. In the medulla the broad ascending limbs of Henle's loop show similar changes while the collecting tubules are practically normal. In all the tubules detritus and casts are found in great numbers. Hyaline, granular and fatty casts are present, but no blood cells or blood casts are present, nor are there any large renal failure casts in the ducts of Bellini.

Interstitial Tissue. Throughout the cortex there is a diffuse production of connective tissue, which, however, leaves scattered areas comparatively free. In the fibrous regions are found the collapsed tubules previously mentioned, and in the latter the hypertrophied ones. Throughout this proliferating connective tissue there is a heavy infiltration with round cells. There is also a definite increase in the connective tissue between the straight tubules of the medulla, but the parenchyma has not suffered particularly from this infiltration.

Arteries. All of the arteries show a moderate fibrous thickening of their intima and around the larger one there is considerable connective tissue proliferation and round cell infiltration. About the thickened branches in the cortex and particularly in the medulla are wide deposits of amyloid.

SUMMARY

The kidneys show a heavy infiltration with amyloid, especially in the glomeruli which are almost totally destroyed by the process. In the epithelium are severe parenchymatous degenerations and there is a marked proliferation and inflammatory infiltration in the interstitial connective tissue.

CASE LVI

John R. Aged forty-eight.

Clinical Diagnosis. Degenerative Bright's disease, pyogenic form.

Duration. Pulmonary tuberculosis for ten years. Edema for three months. Observed during the last month of life.

Etiology. Long-continued lung infection.

Course. Cough and expectoration had persisted for ten years but it was not until nine months before death that weakness and dyspnea on exertion became pronounced. Edema appeared three months before the end. The urine showed an intense albuminuria and all the evidences of a degenerative renal lesion but there was enough renal tissue left to keep the blood urea concentration within normal limits. During the last month there was fever, rapid emaciation and progressive asthenia. On the day of death the blood urea concentration had risen to 421 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

In 1911 cough and expectoration with some loss of weight commenced. For the first seven years the condition was not so pronounced as to prevent him from carrying on some work on his farm, and there were times when he coughed very little and gained in weight. But in 1918 the cough became more persistent and productive and he was no longer capable of hard work. In September 1921 he first noticed swelling of his ankles. The edema gradually increased until he was swollen to the waist. In spite of increasing asthenia it was not until October 1921 that he became so short of breath that he could not leave his bed. He was admitted to the hospital in November 1921. There were signs of an advanced and active tuberculous process in both lungs. The heart was not enlarged. The blood pressure was 98 systolic and 68 diastolic. There was marked edema of both lower extremities and signs of free fluid in the peritoneal cavity. The spleen was easily felt. The patient was emaciated, cyanosed, and very weak.

The urine had a dark brown color but contained no blood. The specific gravity rose at times as high as 1.030. In twelve hours 11,000 mg. of protein were excreted. The number of casts was 330,000 per twelve hours. Of these 1 per cent were epithelial, 11 per cent fatty, 12 per cent waxy and the remainder hyaline sprinkled over with fat droplets. It was not possible to induce diuresis so no exact measurement of the amount of functioning renal tissue was obtained but the blood urea concentration was only 38 mg. per 100 c.c.

During the first ten days in the hospital the edema fluid was excreted. His weight fell from 143 to 100 lbs., and the extreme degree of emaciation became apparent. There was increasing asthenia and it was difficult to feed him. The blood pressure gradually fell and towards the end the systolic pressure was 60 and the diastolic 42. On December 13, six days before his death, there was still no indication of any marked renal decompensation. The blood urea concentration had risen to

71 mg. per 100 c.c. but the urine collected at the same time contained 2.9 per cent of urea. The patient was now moribund. The stools, which were passed involuntarily, contained blood. On December 19, the day of his death, the blood urea concentration was found to be 421 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found an extensive chronic tuberculosis of the lungs. The upper lobes of both were infiltrated with connective tissue and filled with small cavities, while throughout the remaining lobes were more recent scattered tubercles and caseous areas. Both the spleen and liver were enlarged and showed gross evidence of amyloid.

The left kidney was about normal in size, measuring 12 × 6 × 4 cm. Its capsule stripped easily, leaving a smooth surface except for a few small scars along its convexity. In color it was a light yellowish bronze. On the cut surface the cortex was definitely widened and was also a decided yellowish color. The medulla and pelvis were congested, but otherwise negative. Except for some tuberculous ulcers in the lower small bowel, the other organs showed nothing significant. The arteries and heart were normal.

MICROSCOPICAL EXAMINATION

Sections of the liver and spleen showed moderate deposits of amyloid.

Kidneys. *Glomeruli.* The glomeruli are normal size and except for small deposits of amyloid are practically normal. In those in which the masses are larger there is some compression of the capillaries of the tufts, but there is no marked involvement of many of them. Some show a considerable amount of granular material in the capsular spaces, but no red blood cells, leucocytic exudate or other evidence of an inflammatory process is noted.

Tubules. There is a very marked involvement of the epithelium of the convoluted tubules. Practically all show more or less parenchymatous degeneration, varying from moderate degrees of cloudy swelling to instances where the epithelial cells are tremendously swollen and filled with colloid droplets. In scattered areas a marked fatty degeneration is present and in some tubules frank necrosis and desquamation is found. The lumens of almost all the tubules are filled with casts, either hyaline or granular, and in some there is unorganized detritus. No red blood cells are seen, nor any large renal failure casts. The broad ascending limbs of Henle's loop show similar lesions. The epithelium of the collecting tubules is practically normal, though many casts of all sorts are found in their lumens.

Interstitial Tissue. In the cortex there is a slight increase in the interstitial tissue, but not enough to seriously affect the enclosed tubules. An occasional small fibrous scar is present just beneath the capsule. There is also no significant increase in the connective tissue of the medulla. Throughout the cortex, however, there is a beginning infiltration of the interstitial tissue with inflammatory leucocytes. The

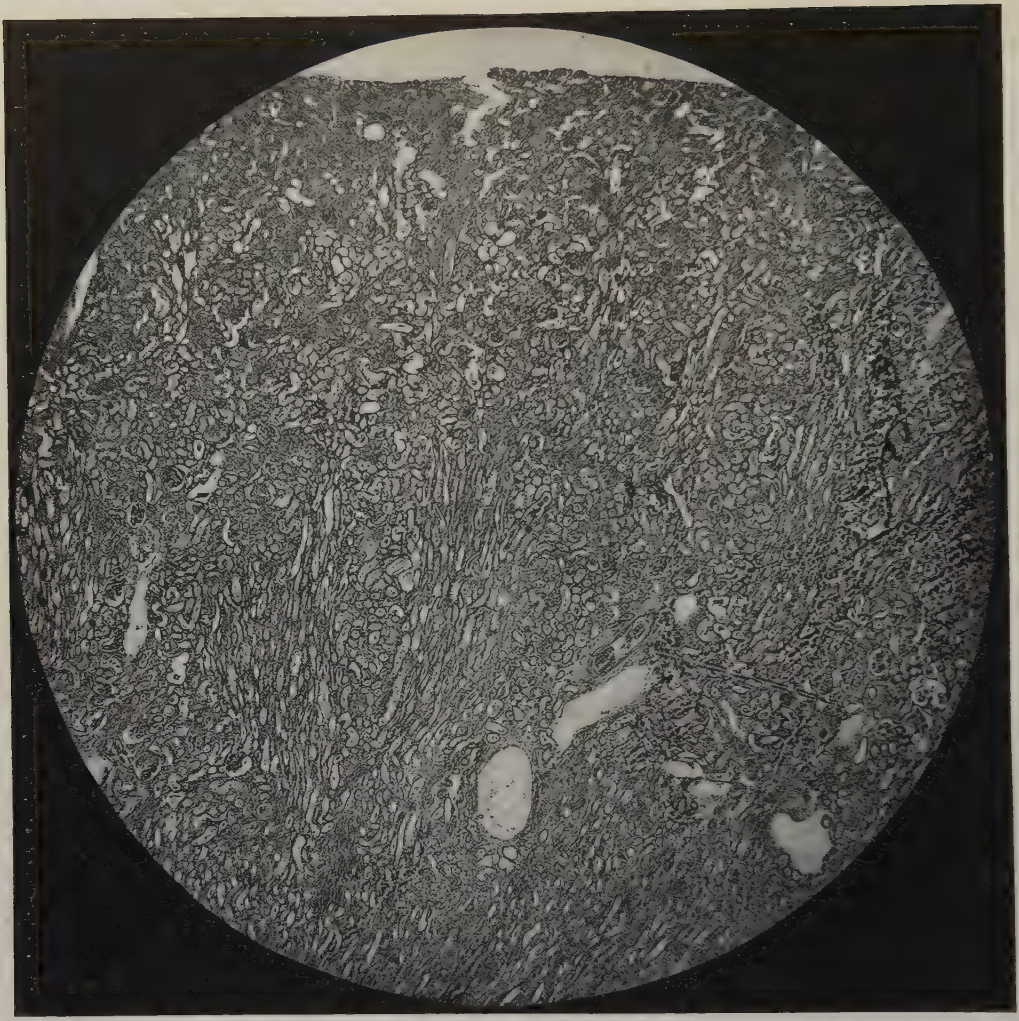

PLATE LVI A

The deposits of amyloid are so small as to escape detection at this magnification. There is a slight diffuse proliferation of the connective tissue throughout the framework of the kidney with some round cell infiltration. The tubules show little atrophic effect of this scarring and are filled with detritus. The arteries are normal.

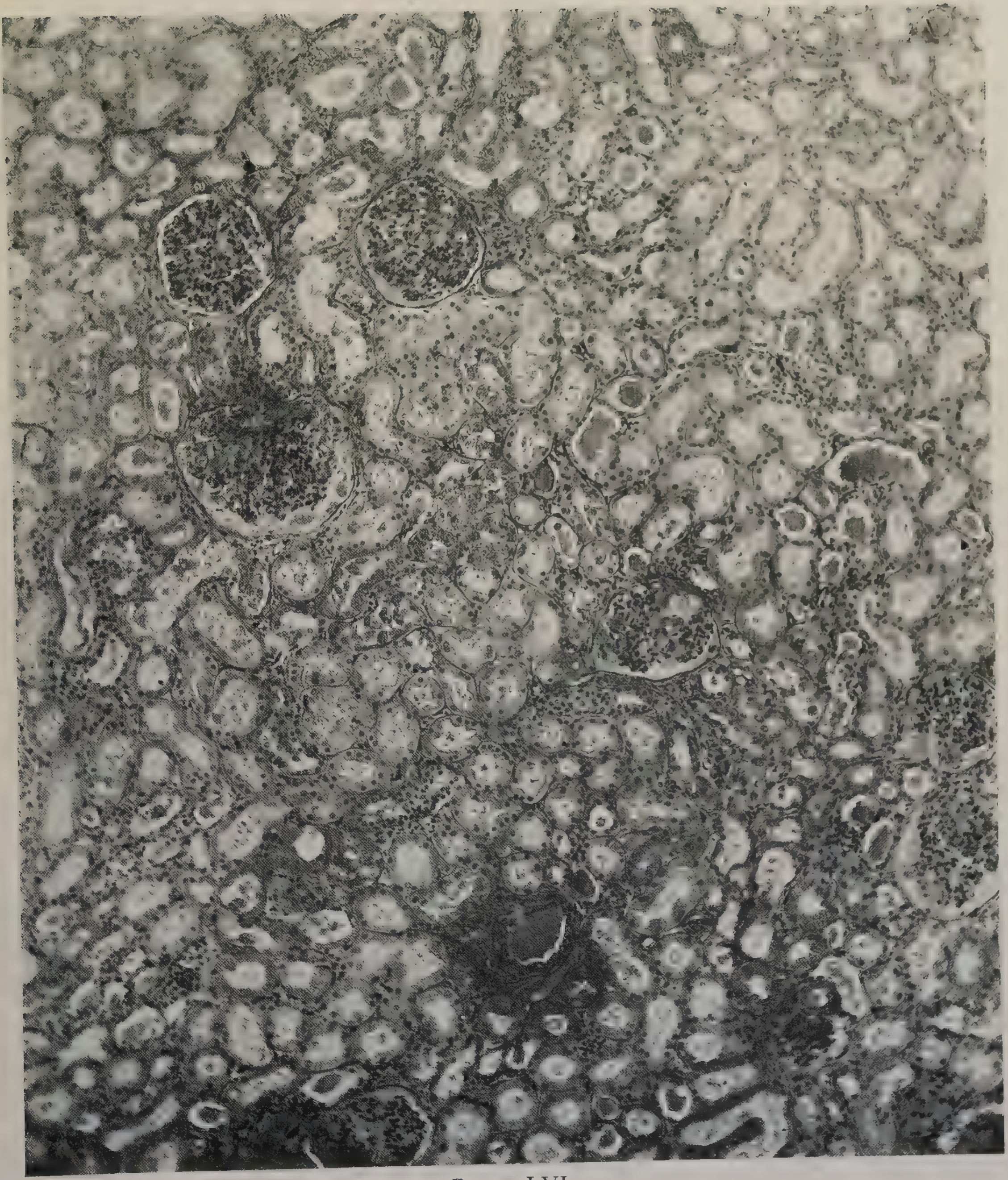

PLATE LVI B

The deposits of amyloid in the glomerular tufts are very small and the inflammatory processes in the interstitial tissue consist of the early stages of leucocytic infiltration with only slight proliferative changes. There are marked degenerative processes in the tubular epithelium.

process is as yet moderate in degree so that there are no large dense areas of involvement such as were found in other examples of this group.

Arteries. The intima of the arteries is not thickened, nor are there any perivascular infiltrations with round cells. The amyloid is deposited around the smaller vessels and capillaries while the larger arteries are free.

SUMMARY

The kidney shows a moderate amyloidosis associated with severe degenerative processes of all sorts in the tubular epithelium of the cortex. There are many casts of all kinds. There is definite evidence of beginning active inflammatory processes in the interstitial tissue. The arteries except for the amyloid infiltration show no significant lesions.

THE BACTERIAL FORM

CASE LVII

Paige C. Aged nine.

Clinical Diagnosis. Degenerative Bright's disease, bacterial toxins.

Duration. Three months or more.

Etiology. Staphylococcus aureus.

Course. For seven years the child had suffered from staphylococcal osteomyelitis in various parts of the body, and had undergone many operations. The urine was reported to be normal towards the end of 1924. In December 1925 generalized edema developed and an intense proteinuria was found. The urine gave evidences of the existence of a very active desquamation of renal epithelium. This was confirmed by two subsequent examinations of the urine. The child died on February 12 after an operation for a perinephritic abscess.

RELEVANT CLINICAL DETAILS

This patient was seen at another hospital and only on one occasion, but three collections of urine were examined, the last of which was obtained thirty-one days before death. We are indebted to Dr. R. G. Flood for the clinical notes and for the opportunity to study the kidneys.

In 1919, while being treated for a boil, symptoms of meningitis developed. A lumbar puncture was attempted and pus was withdrawn from which a pure culture of staphyococcus aureus was obtained. Subsequently *x*-ray evidence of disease of the fourth and fifth lumbar vertebrae was obtained and it seems likely that the lumbar puncture needle had aspirated the pus from a psoas abscess. During the next seven years repeated abscesses developed in various parts of the body. In several instances they were found, when opened, to lead to bone. Whenever a bacteriological examination was made a pure culture of staphylococcus aureus was reported. After each operation there was a long-continuing drainage of pus, so that there were always from two to four open sinuses. In spite of these troubles the child grew and in the intervals between operations seemed well and happy.

Although no doubt many urinary examinations had been made only one urinary report was found before the onset of generalized edema. It was dated in the autumn of 1924 and stated that no albumin or casts had been found.

In July 1925 treatment with gentian violet was begun and during the next five months eight intravenous injections of gentian violet were given, the last on December 5, 1925.

On December 7 the child vomited and was very quiet and listless. Five days later edema of the face was seen and when the urine was examined it was found that it became solid on heating.

On December 17 the patient was seen in consultation with Dr. Flood. There was a slight degree of generalized edema of the skin most marked in the legs. The blood pressure was 119 systolic, and 79 diastolic. The red blood cells were

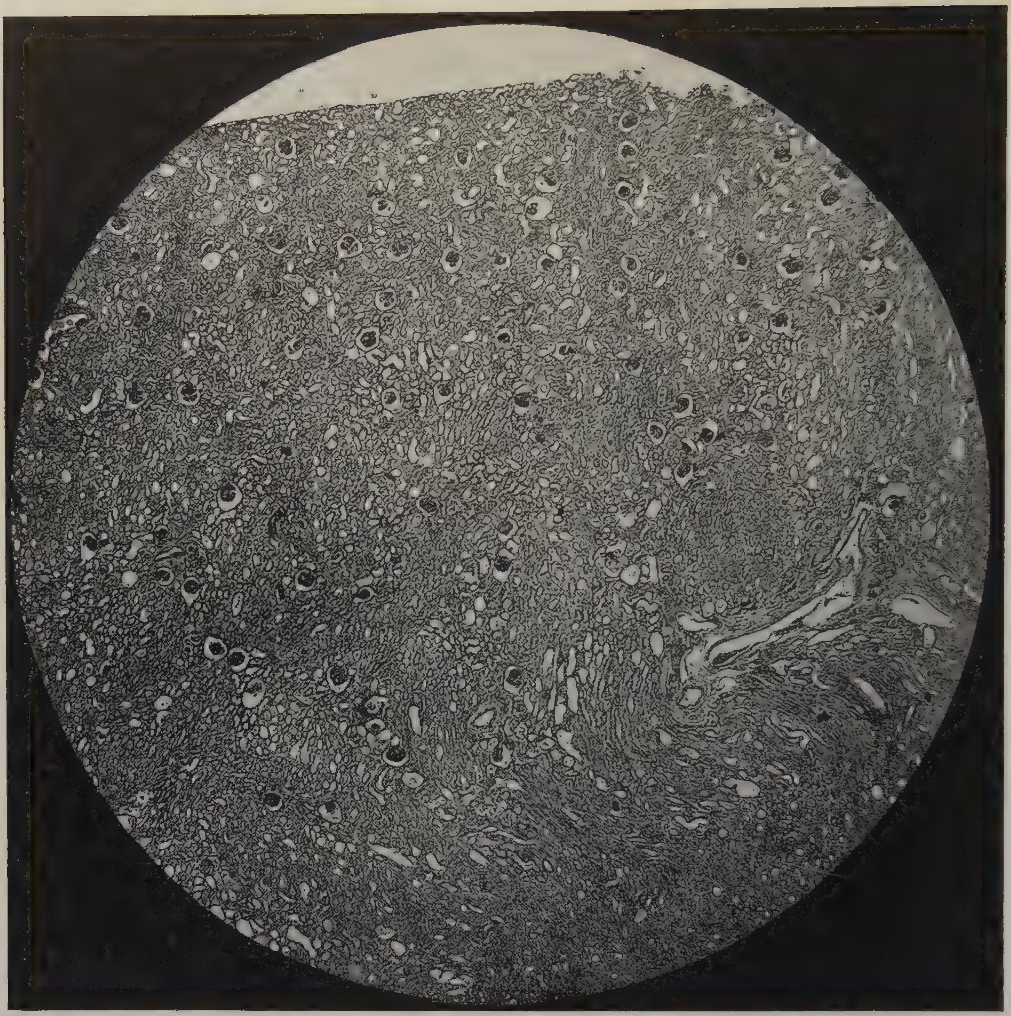

Plate LVII a

There is a moderate but definite proliferation of the interstitial tissue diffuse throughout the cortex. The glomeruli are easily seen as small dark shrunken tufts in various stages of the inflammatory reaction.

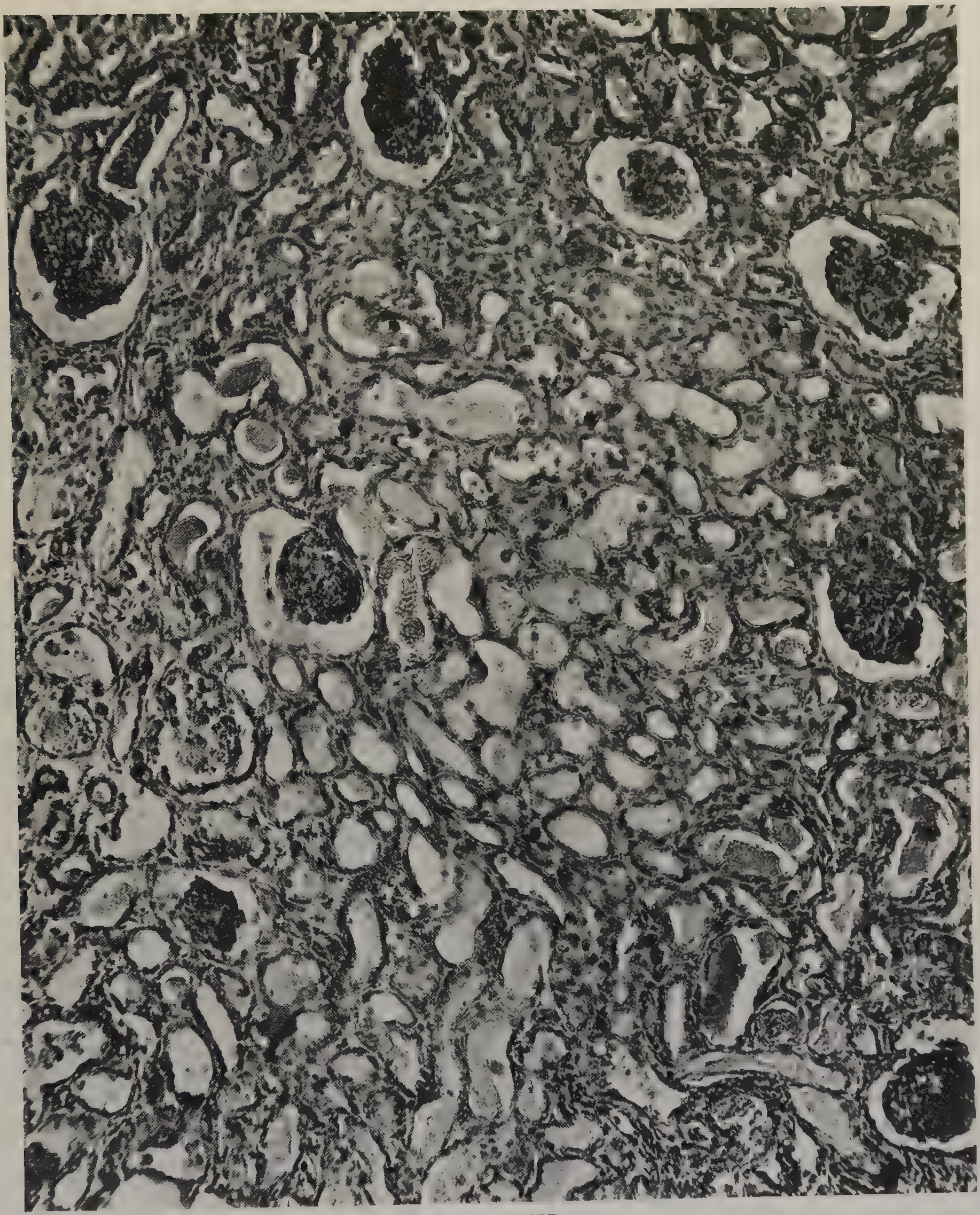

Plate LVII b

The glomeruli are shrunken and distorted by the inflammatory involvement. There is an early inflammatory infiltration of the interstitial tissue. Many casts in the tubules which show varying degrees of distortion and atrophy.

reported as 5,800,000 per cubic millimeter. There was a leucocytosis and a high polymorphonuclear count but no fever. The blood urea concentration was 181 mg. per 100 c.c.

Next day 94 c.c. of urine which purported to be a twelve hour and forty minute collection of night urine under the conditions of the "concentration test" was forwarded from the hospital where the patient was being treated. It was quite opaque and had the appearance of a suspension of globulin precipitated out by carbon dioxide. It solidified firmly on boiling. The concentration of protein was estimated as over 4 per cent, for the rate of protein excretion was 4030 mg. per twelve hours. In the sediment all the casts seemed to be of epithelial origin, or at least were so thickly studded with cells and cellular debris as to be indistinguishable from true cellular casts. The number of casts was 443,000 per twelve hours. A few red blood cells were seen but the count for the twelve hour period was only 312,000, whereas the number of epithelial and white blood cells was 8,400,000. These findings in conjunction with the clinical history led to a diagnosis of a degenerative renal lesion of an unusually intense grade, due in all probability to the staphylococcus.

The edema which was only slight on December 18 had become very marked by the twenty-ninth. By that time also a very definite enlargement of the liver had become evident. It was associated with marked tenderness to palpation in that region. A considerable amount of free fluid had accumulated in the abdominal cavity. The blood urea concentration however had fallen to 72 mg. per 100 c.c. and the blood pressure to 75 systolic and 60 diastolic.

On January 12, 1926 another timed collection of urine was obtained. The volume was 243 c.c. per twelve hours and the specific gravity was 1.024. The protein concentration was still very high and the urine was still opaque, apparently from the precipitation of globulin. The rate of excretion of protein for twelve hours was 3171 mg. In twelve hours 1,815,000 casts were excreted. Of these 5 per cent were epithelial, 67 per cent granular, 5 per cent waxy and 23 per cent hyaline. No red blood cells were seen, but there were a very large number of white blood and epithelial cells. The estimate was 26,000,000 in twelve hours.

On the following day the fifth lumbar vertebra was exposed, a sequestrum removed and an abscess evacuated. A staphylococcus aureus was obtained in the culture.

There was a rapid decrease in the edema and albuminuria after this operation but on January 21 the drainage increased and the routine tests showed an increase in the concentration of protein in the urine. Signs of a new abscess in the lumbar region began to develop.

Another timed urine collection was examined on January 28. It was cloudy and opaque. The volume was 263 c.c. per twelve hours, the specific gravity 1.018. On centrifugalizing there was a very large volume of sediment but the supernatent fluid remained cloudy. The rate of protein excretion was 5681 mg. per twelve hours. The number of casts per twelve hours was 7,900,000. Most of the casts, 65 per cent it was estimated, were granular and 24 per cent waxy. Some of the casts were definitely of the renal failure type. Measurements were made and it was found that 12 per cent were 40 or more microns broad (usual average about 20 microns). No red blood cells were seen, the large sediment consisting of white blood and epithelial cells. From the counts it appeared that there were about 601,000,000 of these cells in the twelve hours' urine.

Next day (January 29) a perinephritic abscess (staphylococcal) was opened at the lower pole of the right kidney. The kidney was partially decapsulated. For some days after the operation the volume of urine was reduced to about 50 c.c. per twenty-four hours. The child became blind on February 1. Ophthalmoscopic examination revealed numerous fresh retinal hemorrhages. There was later some return of vision and an increase in urine volume, but there was no recovery of strength and on February 12, 1926 the child died, apparently from asthenia.

PATHOLOGICAL OBSERVATIONS

The kidneys only were obtained after death. They were of normal size and their capsule stripped easily, leaving a fairly smooth greyish pink surface. No hemorrhages were seen. The cut surface except for some swelling and opacity of the cortex was normal. The pelvis and arteries were normal.

MICROSCOPICAL EXAMINATION

Glomeruli. In practically every glomerulus are small patches of fibrosis in which the capillaries are obliterated. The tufts are distorted; in some is a leucocytic infiltration with mononuclears and polymorphonuclears and in many there are adhesions to the parietal wall of Bowman's space. In the space is granular material and occasionally exudate and a few red blood cells, but definite crescents are rare.

Tubules. Most of the convoluted tubules of the cortex show evidence of severe damage. Their lumens are filled with a detritis of desquamated epithelial cells, leucocytes and granular material. The epithelium is in all stages of various degenerative processes from extreme cloudy swelling to frank necrosis. This change is most pronounced in the terminal portions of the convoluted tubules and the broad ascending limbs of Henle's loop. Other tubules are lined with very atypical newformed cells which form an irregular covering for the membrana propria. There are many casts of all sorts in all the tubules, but in greatest number in the straight tubules of the medulla.

Interstitial Tissue. Throughout the cortex is a diffuse cellular proliferation of the interstitial fibrous connective tissue, which widely separates the tubules and glomeruli from each other. The cellular constituents of this tissue are principally fibroblasts though a few scattered round cells are present. The tubules and glomeruli have not yet suffered much distortion from the newly developed tissue, so there is neither collapse or dilatation of them.

Arteries. All the arteries are normal.

SUMMARY

The kidney shows extensive degenerative changes in its epithelial structures, with regenerative repair and active inflammatory processes in the glomeruli and nterstitial tissue.

THE NON-BACTERIAL FORM

CASE LVIII

Adam B. Aged sixty-two.

Clinical Diagnosis. Degenerative Bright's disease. Non-bacterial toxins: jaundice, arsphenamine and mercury.

Duration. One and one-half months.

Etiology. Arsaphenamine, mercury and jaundice.

Course. On March 18, 1920 he came to the hospital complaining of recurrent attacks of pain in the right hypochondriac region. The liver was enlarged. Routine urine examination showed no albumin or casts. The Wassermann reaction was positive. On April 1, 1920, he was given 0.6 gm. of arsphenamine intravenously. On the next day he was slightly jaundiced but by April 14 the jaundice had disappeared. Between that date and May 14 he received six doses of arsphenamine and five intramuscular injections of gray oil. On May 14 it was noted that he was deeply jaundiced and some degree of jaundice had been observed by the patient some days previously. The blood urea rose very rapidly from 180 mg. per 100 c.c. on May 17 to 556 mg. per 100 c.c. on the day of his death on May 21. The urine was small in amount, not of low specific gravity, and contained a large number of renal failure casts and epithelial cells.

RELEVANT CLINICAL DETAILS

The patient was seen first in February 1918 when he came complaining of dimness of vision which was due to a cataract. He had a moderate degree of hypertension and arteriosclerosis without symptoms. Two routine examinations of the urine failed to show any casts or albumin.

On March 18, 1920, he returned complaining of recurrent attacks of pain in the right hypochondriac region which was sometimes severe and accompanied by vomiting. There was no history of jaundice. There was much muscle spasm and tenderness in the gall bladder region. The edge of the liver could be felt well below the costal margin. The Wassermann reaction was positive. No albumin or casts were found on a routine examination of the urine.

On April 1, 1920, he was given 0.6 gm. of arsphenamine intravenously. There was no reaction but next day he was slightly jaundiced and complained of abdominal pain. On April 7 he was still jaundiced. Gray oil was given intramuscularly. On April 14 no trace of jaundice remained and between that day and May 23 he was given six arsphenamine injections and four injections of gray oil.

Probably on May 10 the jaundice returned. On the fourteenth when he was admitted to the hospital he was deeply jaundiced, and complaining of severe constant pain in the upper abdomen which had kept him from sleeping for the preceding two nights. The liver was greatly enlarged and the edge could be felt nearly at the level of the umbilicus. There was some free fluid in the abdominal cavity. There was fever and polymorphonuclear leucocytosis. The patient was obviously in a very toxic state, and became cyanotic on exertion. During the next

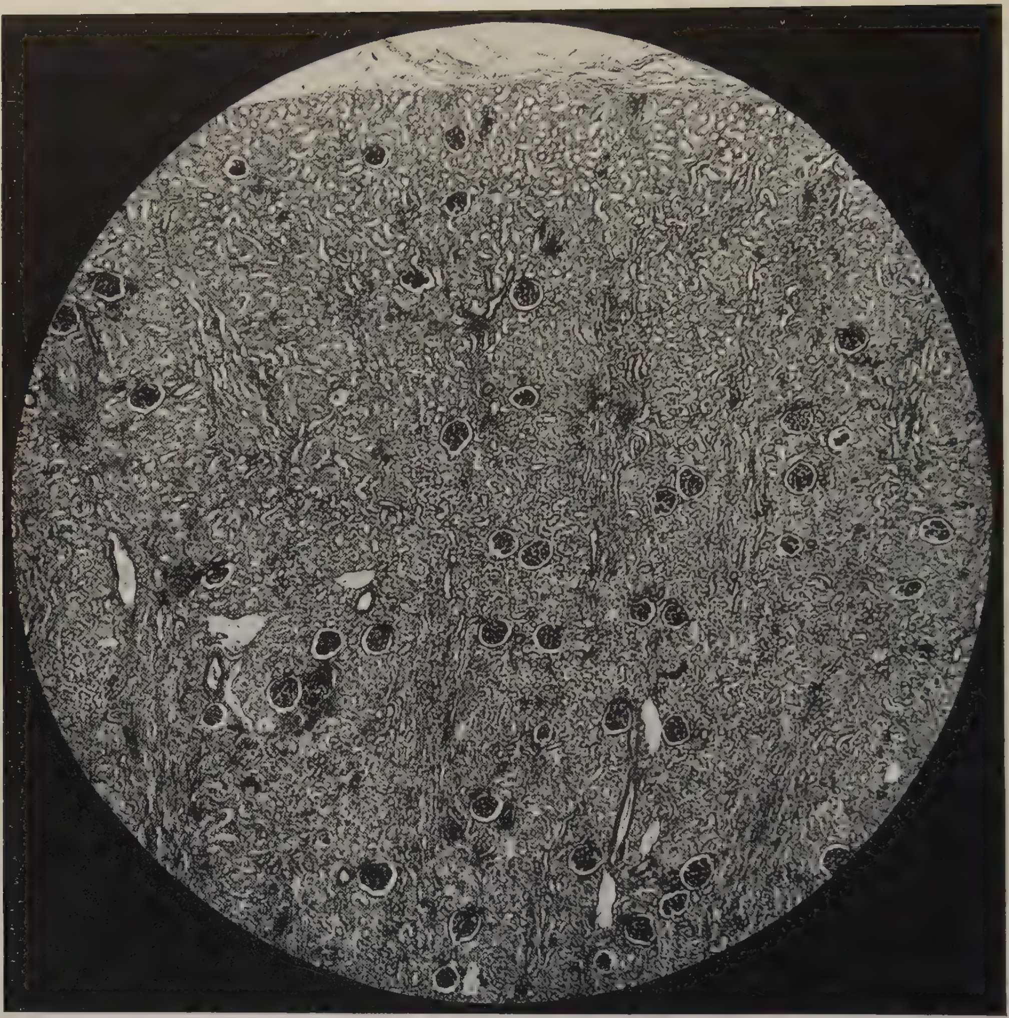

Plate LVIII a

The glomeruli are well preserved and the interstitial tissue, except for a few irregular sclerotic scars which bear no relation to the significant lesion, is normal. The acute degenerative changes in the tubular epithelium do not show plainly at this magnification. (Cf. Plate lxxiv.)

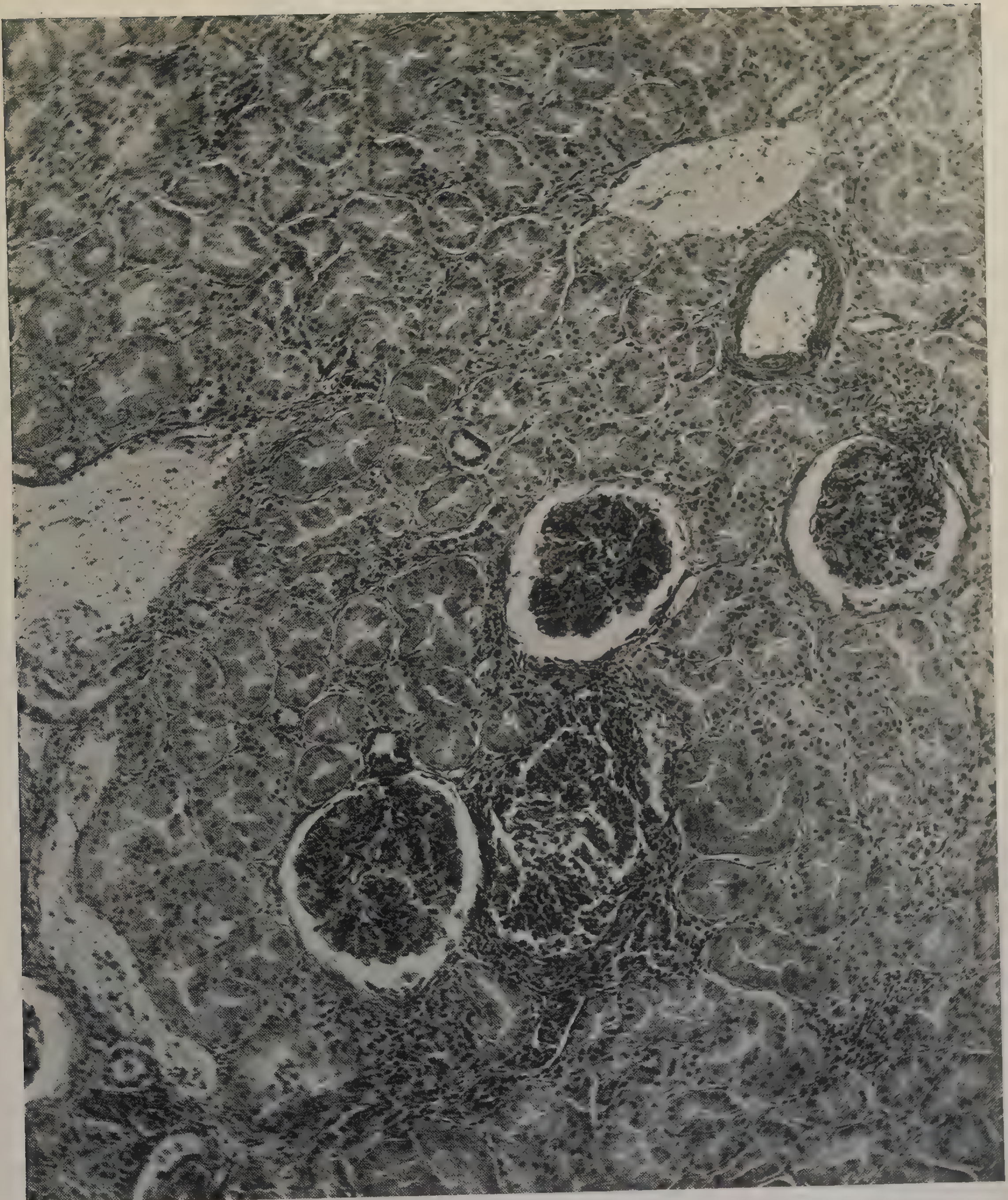

Plate LVIII b

There is a slight increase of the nuclei in the glomerular tufts and irregular scattered round cell infiltration in the interstitial tissue. There is a marked cloudy swelling of the tubular epithelium. An artery is seen to be normal.

few days there were several severe nosebleeds and recurrent prolonged attacks of hiccoughing. On May 19 a small amount of urine was collected. From 10 c.c. a deposit which occupied a volume of about 0.05 c.c. was obtained which consisted of deeply bile-stained renal failure casts and epithelial cells mixed with mucus. The casts were all of the coarsely granular variety, short, and of rather uniform breadth. There were few if any red blood cells.

The patient became weaker and drowsy. On May 17 the blood urea concentration was 180 mg. per 100 c.c.; on May 19, 312 mg.; on May 20, 409 mg. and on May 21, the day of his death, the concentration had risen to 556 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

At autopsy a large oval cholesterin stone was found in the common duct about 2 cm. above the papilla of Vater. The obstruction it had caused was apparently intermittent as the contents of the large bowel were clay colored whereas that of the duodenum and jejunum was bile stained. The gallbladder was infiltrated with a dense hard tumor mass. The liver except for the jaundice was grossly normal.

The left kidney was enlarged, measuring 13 × 8 × 5 cm. The capsule stripped fairly easily, leaving a finely granular icteric surface. The cut surface showed a marked icterus and the cortex was very opaque and soft. The pelvis and medulla were bile stained, otherwise normal. The right kidney was the same as the left. Except for a luetic aortitis of moderate degree and the general icterus no other significant lesions were found.

MICROSCOPICAL EXAMINATION

Sections of the gallbladder showed its wall diffusely infiltrated with carcinomatous tissue. The liver showed a marked icterus and beginning necrosis of the icteric centers of the lobules.

KIDNEYS. *Glomeruli.* The glomeruli are practically normal. The capillary tufts are somewhat congested and occasionally some fine granular material is seen in Bowman's space, but no evidence of any inflammatory or degenerative process.

Tubules. The shape of the convoluted tubules in the cortex is normal except that they are somewhat large. This is due to a swelling of the epithelium which is very granular. In some places there is a frank necrosis and desquamation of the epithelial cells. A distinct icteric discoloration of the epithelium and necrotic material can be seen in some places. Scattered among the areas of degeneration and necrosis are tubules lined with a darkly staining irregular layer of regenerated cells. The lumen of the tubules contains besides the detritus a moderate number of hyaline and granular casts. Some of these are also yellowish green. The broad ascending limbs of Henle's loop show the same changes, while the collecting tubules, except for the presence of broad casts, are normal.

Interstitial Tissue. Scattered throughout the cortex are a few very small scars. They are insignificant, however, when compared to the large amount of cortex which is not involved. Irregularly scattered throughout the cortex are areas of rather dense leucocytic infiltration. Most of the cells are of the mononuclear type.

Arteries. There is a moderate fibrous thickening of the intima of the larger arteries and a slight round cell infiltration about some of them.

SUMMARY

The kidneys show widespread degeneration and scattered necrosis of the epithelium of the convoluted tubules and Henle's loop. There is no evidence in them or in the liver of damage by either mercury or arsenic, although these substances may have produced some effect along with the icterus, which was evidently the chief cause of the epithelial damage. The glomeruli and arteries are essentially normal. In the interstitial tissue is an early inflammatory infiltration with leucocytes.

CASE LIX

Alonzo P. Aged thirty-five.

Clinical Diagnosis. Degenerative Bright's disease, non-bacterial toxins, malaria.

Duration. One week. Observed during the last two days.

Etiology. Malaria.

Course. An intense malarial infection was followed by anuria for four days. During the next three days small amounts of urine were excreted but the blood urea concentration rose to high levels and the patient died seven days after the onset.

RELEVANT CLINICAL DETAILS

A sailor who had just arrived in San Francisco from Mexico by sea consulted a doctor on account of inability to void urine for twelve hours. His temperature was 101°F. and he complained of severe pains in the legs. Only a few drops of deep yellow urine were obtained by catheter. A specimen of blood showed an uunusally heavy malarial injection. It was reported that ring forms but no crescents were seen.

He was seen two days before his death. He was then deeply comatose. The blood urea concentration was 305 mg. per 100 c.c. The blood pressure was 110 systolic and 80 diastolic. The temperature was 101°F. The urine obtained by catheter had a deep orange color but the concentration of urea in the urine was only 0.6 per cent. Protein was present but not in very high concentration. A timed urine collection was obtained later and it was estimated that there were 15,000,000 red blood cells and 5,700,000 white blood cells and epithelial cells excreted per twelve hour period. Most of these cells were stained deep yellow. The number of casts was 310,000 per twelve hours. With the exception of about 4 per cent hyaline casts they were all renal failure casts but were peculiar in respect to their dark orange color.

On the next day the blood urea concentration had risen to 422 mg. per 100 c.c. and the patient died in deep coma.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained at autopsy. They were of normal size. Their capsules stripped easily, leaving a smooth greyish pink surface in which no hemorrhages could be seen. The cut surface showed a marked opacity and widening of the cortex. The renal arteries show no definite thickening.

MICROSCOPICAL EXAMINATION

Glomeruli. In all of the glomeruli the tufts are well preserved and show no definite abnormalities. Bowman's space is free of fibrinous exudate but in the majority precipitated granular material can be seen.

Tubules. All of the convoluted tubules throughout the cortex and their spiral terminal portions which extend into the outer zone of the medulla are the seat of active degenerative processes. Their epithelial cells are swollen. The protoplasm is granular and though the nuclei are preserved in most instances in some cells pycnosis of these structures with necrosis and desquamation has occurred. The same lesions are found in the broad ascending limb of Henle's loop. In the lumen of the tubules in the cortex is a large amount of granular debris which has the same appearance as the granular material which is seen in Bowman's capsule. In some of the tubules recently shed red blood cells are found. Very few definitely formed casts are present in the tubules of the cortex but in many of the large collecting tubules and ducts of Bellini are broad renal failure casts. There are many desquamated cells included in these formations.

Interstitial Tissue. The interstitial tissue throughout the cortex is normal except that there are a few small scattered rather cellular scars.

Arteries. There is a moderate fibrous thickening of the intima of the arcuate arteries and the same lesion may be found in a few of the smaller interlobular branches.

SUMMARY

The kidney shows marked degenerative lesions in the epithelium of the tubules and evidence of simple glomerular damage in the leakage of protein through its membrane. There is also present a slight arteriosclerosis with some small scars in the interstitial tissue. Renal failure casts are present.

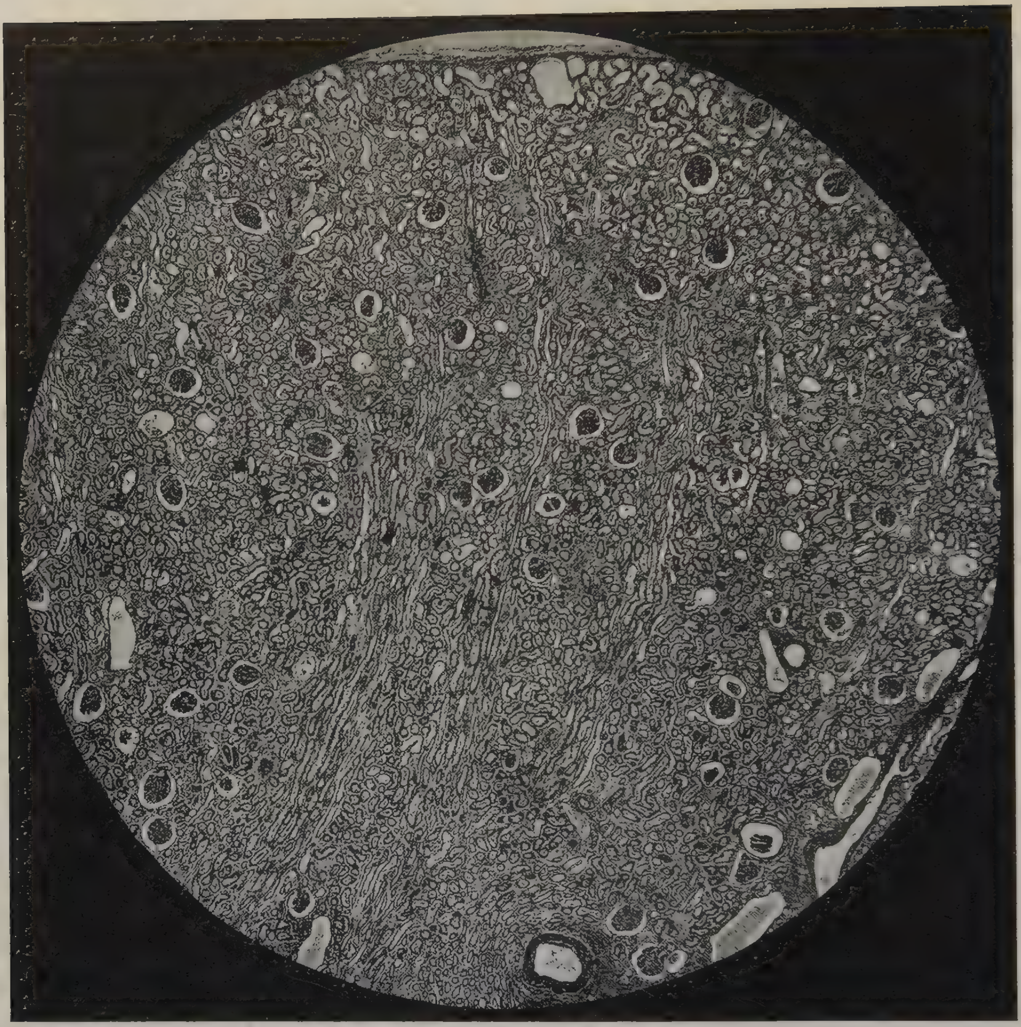

Plate LIX a

Associated with the tubular degeneration which is obvious from the detritus which fills all of the tubules is a moderate sclerosis of the renal artery. There are a few small fibrous scars, a result of the vascular lesion. The glomeruli are well preserved.

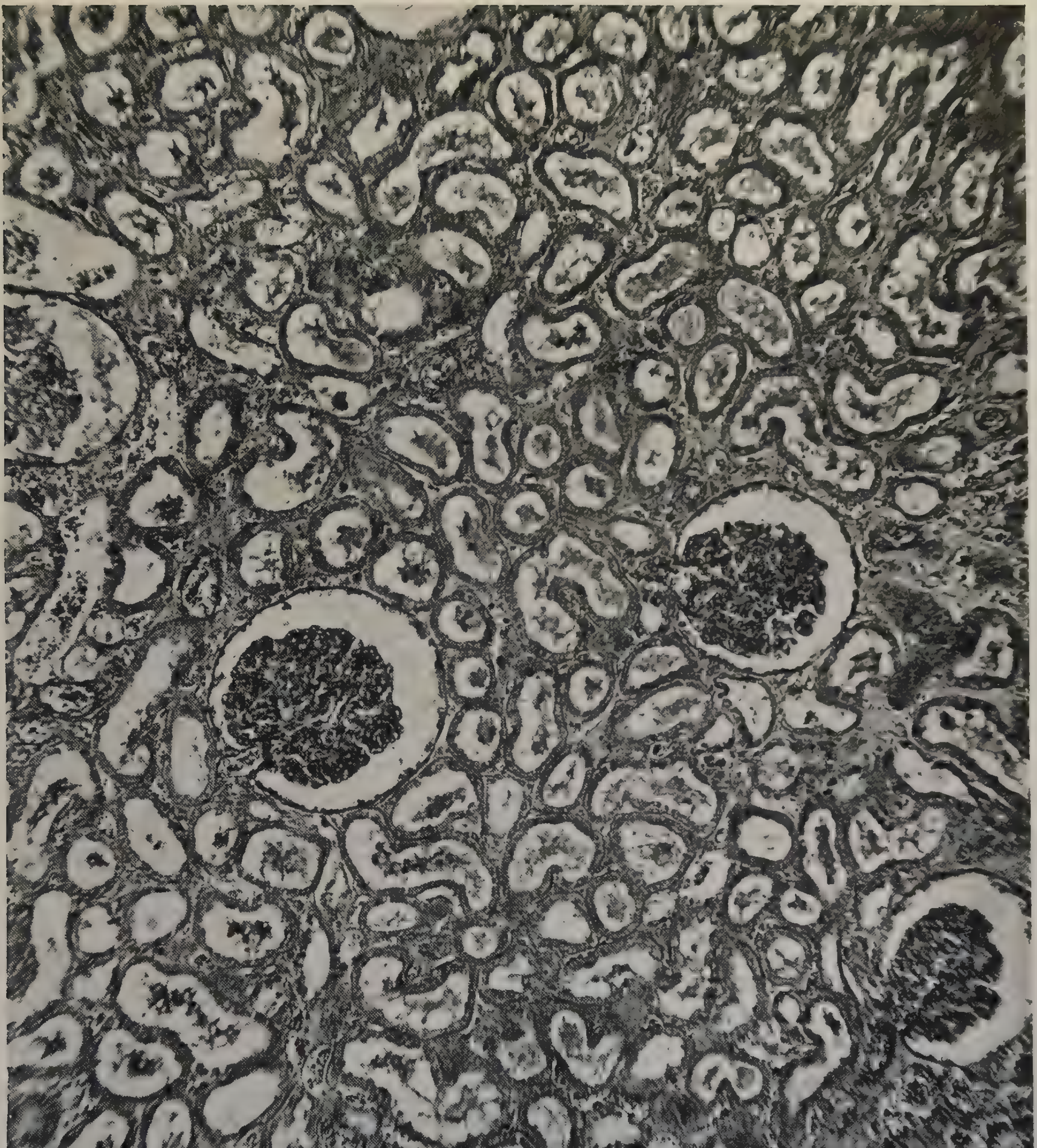

Plate LIX b

The glomerular tufts are essentially normal but granular material is seen in Bowman's space. There are various degenerative changes in the tubular epithelium and their lumens contain coagulated granular material. The interstitial tissue shows no significant lesions. (Cf. Plate lxxviii.)

ARTERIOSCLEROTIC BRIGHT'S DISEASE

CASE LX

Leonard C. Aged thirty-five.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Duration. Unknown. Observed during the last six days.

Etiology. Unknown.

Course. Hypertension had been noted five months before death but for how long a period it had previously existed is not known. The patient died of cardiac decompensation with acute suppurative parotitis as a complication. On the day before his death the blood urea concentration had risen to 278 mg. per 100 c.c. but the urinary examination suggested that the lesion in the kidney was arteriosclerotic and did not represent the terminal stage of glomerular nephritis.

RELEVANT CLINICAL DETAILS

In December 1924 he had for a few days paroxysmal attacks of dyspnea with tachycardia, cough and expectoration of thick brown sputum. The doctor told him that his systolic pressure was 210 and that there was something wrong with his lungs. He recovered rapidly. In January 1925 these symptoms recurred and since then he had suffered from increasing cardiac disability. On April 1 his legs became swollen and on April 6 he became irrational and began to have Cheyne-Stokes' respiration. He was admitted to the hospital on April 12. Examination of the lungs disclosed slight dulness with moist râles at the right base. Over the left lung moist râles were heard at the base and over an area anteriorly between the second and fourth ribs. There was no bronchial breathing. The heart was greatly enlarged. The radial arteries did not seem to be thickened. There was no note of arteriosclerosis of the retinal arteries but a few small hemorrhages were seen. The blood pressure was 195 systolic and 145 diastolic. The hands and feet were blue and there was edema of the legs to above the knee. There was no anemia. A count of the red blood cells gave 5,850,000 per cubic millimeter. On the day after admission an acute suppurative parotitis developed. Routine urine examinations had shown that the urine contained much albumin and many casts. On April 17 the blood urea concentration was found to be 378 mg. per 100 c.c.

The urine was not examined until April 18, the day of his death. The patient was then deeply comatose but 34 c.c. of urine were obtained by catheter. The specific gravity was 1.027. The concentration of protein was 0.8 per cent. The sediment contained large numbers of epithelial and granular casts of normal breadth, though among them some renal failure casts were seen.

These urinary findings seemed sufficient to exclude uremia due to a primary kidney failure. The high blood urea concentration seemed to receive a possible explanation from the fact that an adequate amount of fluid could not be given so that the toxemia resulting from the parotid infection was combined with dehydration. The evidence of desquamation of renal epithelium was what might be expected as a result of a degenerative lesion due to infection. The absence of any increase

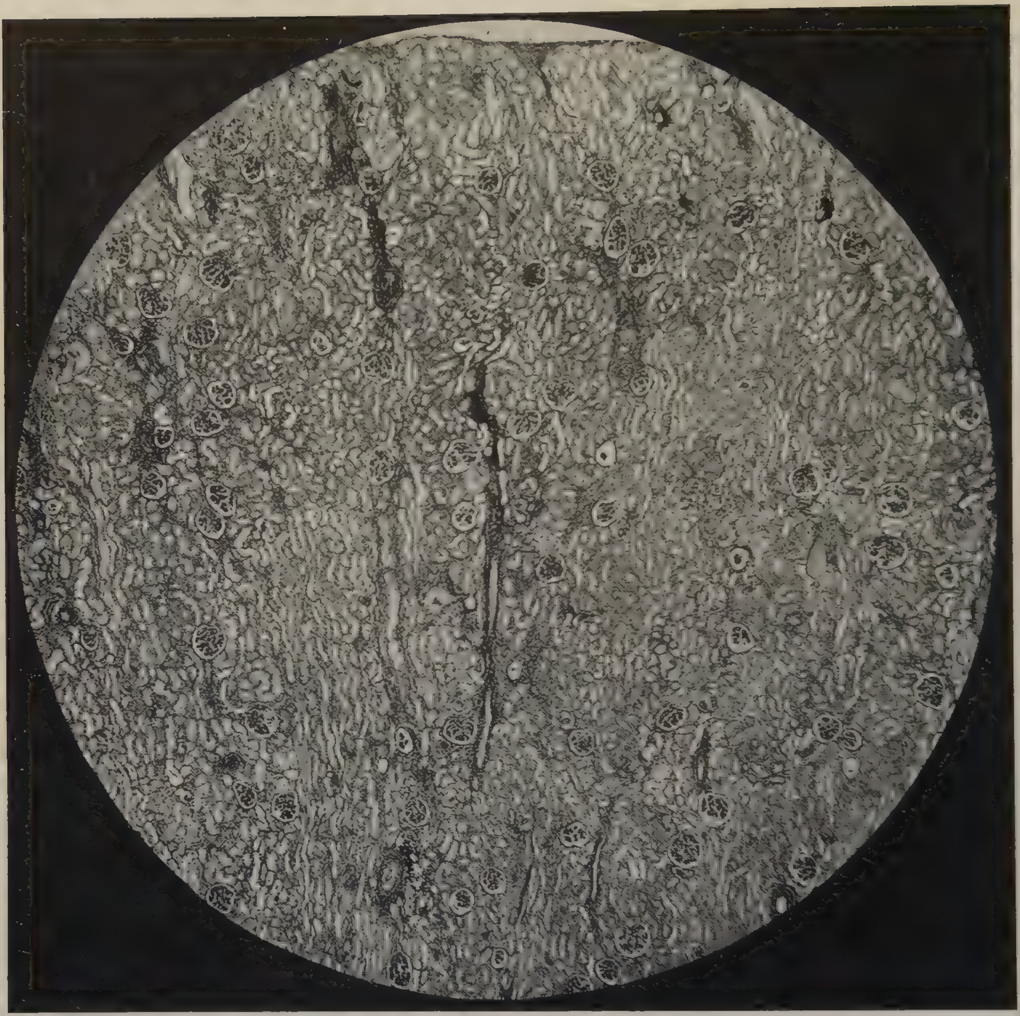

Plate LX a

The moderate thickenings of the cortical branches of the renal artery can be seen throughout the section. There are a few small scattered irregular scars. Most of the glomeruli are fairly well preserved and since the connective tissue proliferation in the framework is moderate, the arrangement of the tubules has not suffered.

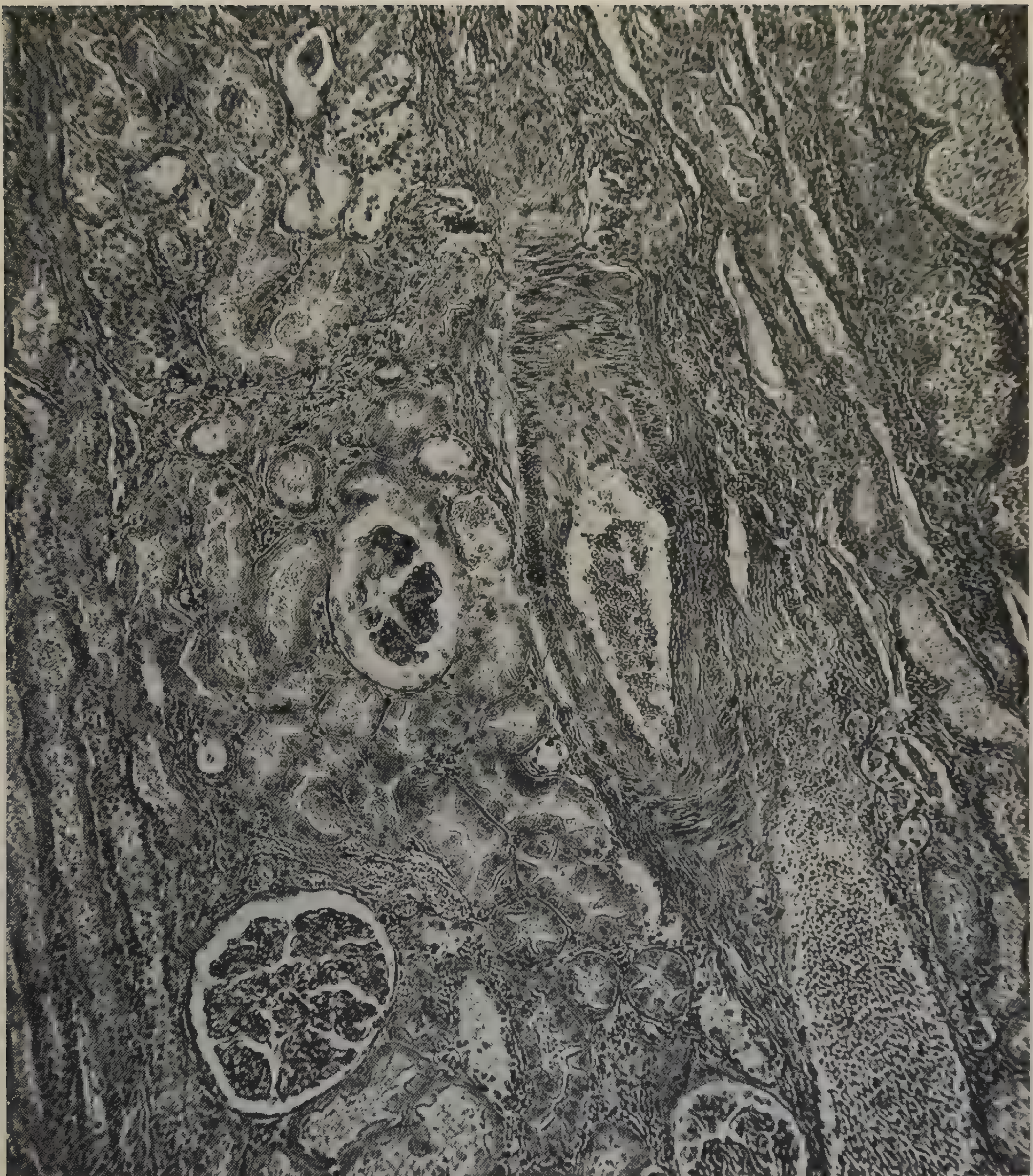

Plate LX b

The glomerular tufts in the section are not involved. There is some proliferation of the interstitial tissue with round cell infiltration. A small artery shows a marked sclerosis.

in red blood cells in the urine excluded hemorrhagic Bright's disease. In view of the history and the facts disclosed by physical examination a diagnosis of renal arteriosclerosis was made.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were available for postmortem examination. They were of normal size, measuring 12 × 6 × 4 cm. Their capsules stripped fairly easily, leaving a reddish purple surface in which were a few retracted scars. The cut surface showed no very apparent abnormalities. The renal arteries were definitely thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Most of the glomeruli are normal. The tufts are not fibrous, the capillaries are patent, and Bowman's space is empty. Those glomeruli which are enclosed in scar tissue are compressed however, and in some there is a development of fibrous connective tissue which more or less obliterates the tuft. The number of glomeruli so involved as compared to the normal ones is small.

Tubules. All of the convoluted tubules and broad ascending limbs of Henle's loop show a marked parenchymatous degeneration. There is a cloudy swelling of the epithelial cells of the milder type. Their nuclei are well preserved but the protoplasm is swollen and of a ground glass appearance without the accumulation of definite granules. The lumen of these tubules contains large amounts of granular material, while in the straight tubules definite hyaline and granular casts are found. No red blood cells or leucocytes are present.

Interstitial Tissue. Throughout the greater part of the cortex the interstitial tissue is normal. There are however scattered areas where scars are formed by a fibrous proliferation of tissue which is still cellular and which contains a few round cells. Where these reach the free surface of the kidney superficial retracted scars are formed.

Arteries. There is a moderate fibrous thickening of the intima of the arcuate and larger arteries. The smaller branches to the cortex are somewhat more prominent than normal due to a thickening of their walls, but the arterioles to the glomeruli are in most cases normal.

SUMMARY

The kidney shows a moderate arteriosclerosis which has not involved many of the glomerular arterioles. There are a few fibrous scars in the interstitial tissue, and a widespread recent cloudy swelling of the epithelium of a recent mild type.

CASE LXI

Edward G. Aged twenty-four.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Duration. More than five years.

Etiology. Unknown.

Course. In 1924 when he began to suffer from headaches an examination of the urine revealed an albuminuria. In February 1929 after an exceptionally severe headache he became unconscious and for a week thereafter remained in a stuporous state. There was an ocular paresis, marked hypertension and albuminuria. He was seen in June 1929 when he was free from all subjective symptoms, but had a systolic pressure of 230 and a diastolic of 180. There was a moderate albuminuria and cylinduria (hyaline casts only) but no evidence of a hemorrhagic or degenerative renal lesion. On August 5, 1929 he had a generalized convulsion and died while unconscious some hours later.

RELEVANT CLINICAL DETAILS

His family history was fairly well known but there was nothing to suggest any tendency towards arterial disease. In 1911, when six years old, he was jaundiced and was somewhat weak and undernourished for some years afterwards. In 1916 during an acute appendicitis some casts were found in the urine but there was said to be no albumin. His general health improved after the appendix was removed and he was an athletic healthy young man of nineteen years of age when in 1924 he began to suffer from headaches. He consulted a doctor who examined the urine and told him that there was "something wrong with his kidneys." The headaches persisted intermittently but he was inclined to ascribe them to alcohol, for he had now fallen into the habit of taking six to eight drinks a day, and the headaches were never sufficiently severe during the next five years to make him lose any day of work. It was not until some time in January 1929 that he had to stay in bed for several days on account of severe headache which was accompanied by great weakness and profuse perspiration. On February 23, 1929, during dinner he had a sudden feeling that he was going to vomit but in a few minutes it had gone as suddenly as it came and he finished the meal.

On February 26, 1929, the first really alarming symptoms developed. During the afternoon a dull headache grew more and more intensely painful and about 8 P. M. he found that his legs were slow and heavy and his hands trembling. He felt dizzy and soon afterwards vomited. He went slowly to his bedroom and tried to get his clothes off but he did not succeed, for some hours later he was found half undressed, in a deeply unconscious state. He was far from home but his mother saw him two days later. He lay still with closed eyes and would not answer questions but the doctors told her that there was no evidence of paralysis except for a squint. There was a very high blood pressure, albuminuria and casts in the urine, but no edema. He gradually came back to consciousness but even a week later he was still

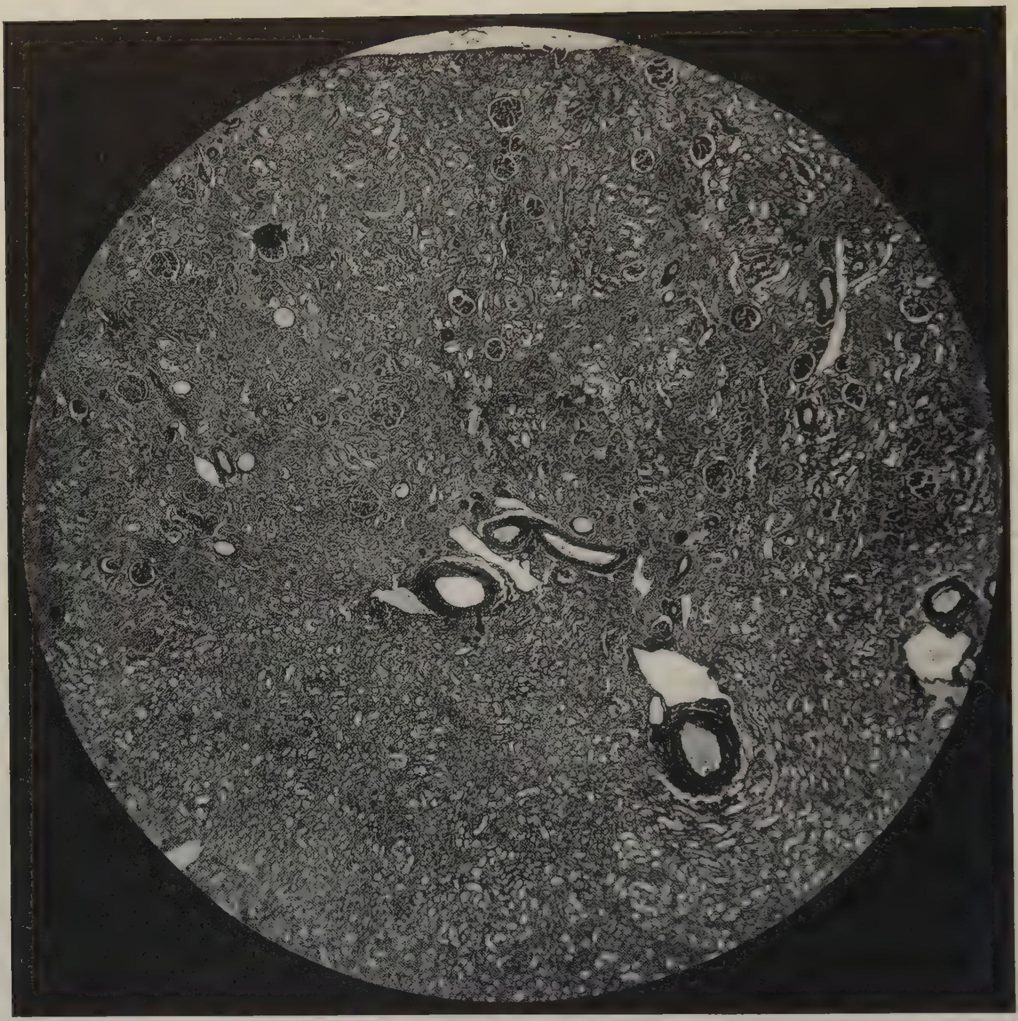

PLATE LXI A

Several large thickened sclerotic vessels are scattered through the section and the smaller branches to the cortex also stand out prominently. There is a diffuse proliferation of the connective tissue with scattered infiltration of round cells. Many glomeruli are still fairly well preserved but the atrophy and distortion of others is clearly evident.

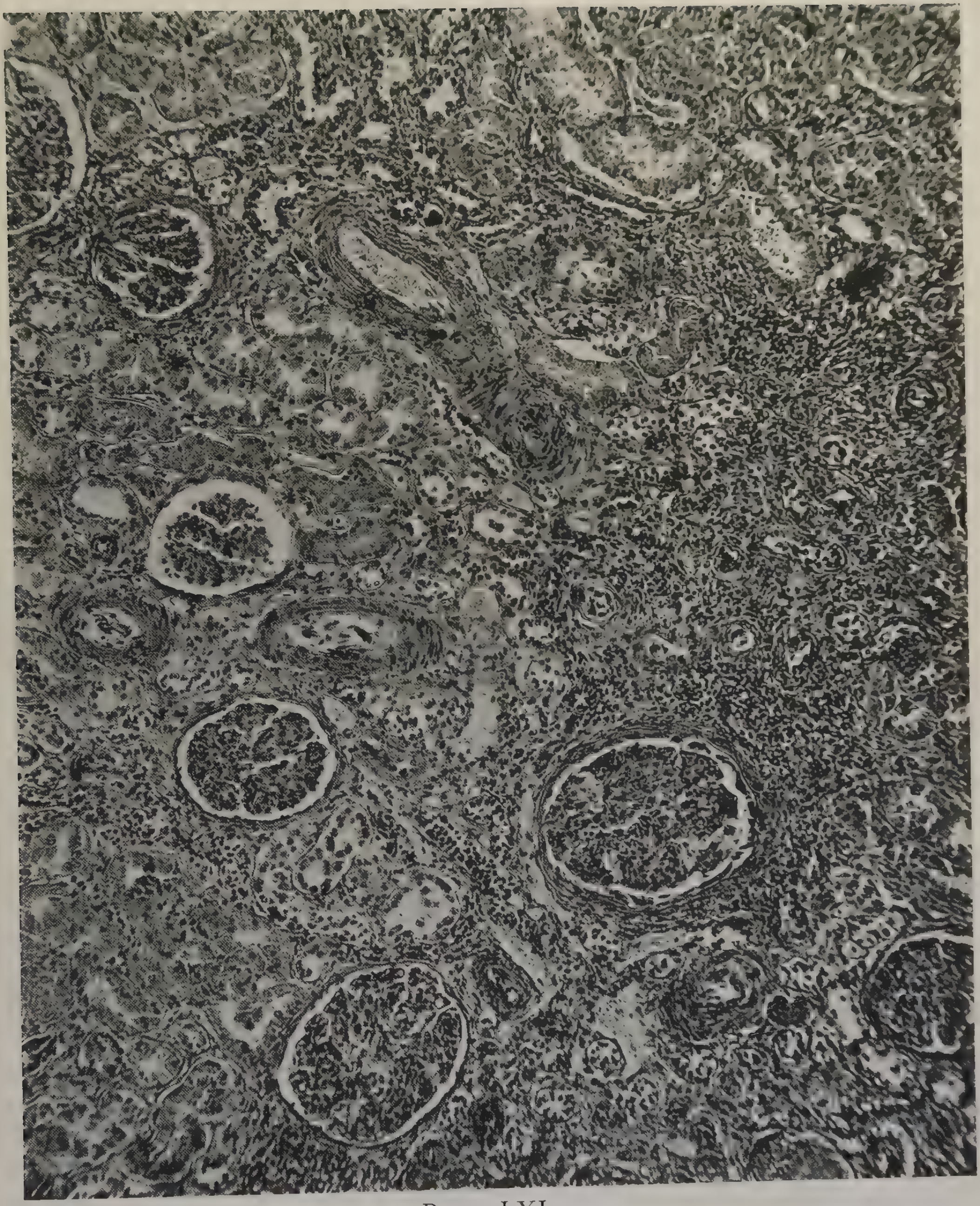

Plate LXI b

The sclerotic vessels are well shown. There is extensive scarring of the interstitial tissue with heavy round cell infiltration. The glomeruli are still very well preserved and there are various types of degenerative change in the tubular epithelium.

drowsy and lethargic. The squint however was gone in a few days. He was very tired and willingly remained in bed for about two months. But the headaches had gone and he came slowly back to a condition which was appreciably better than he was in before. However, Dr. Wallace Wilson who was observing him at this time found that his diastolic pressure never fell below 150.

When he was seen in Vancouver on June 25, 1929, he stated that he felt entirely well, in fact better than he had ever felt before. He had been back to work for several months and was able to play hard tennis. His blood pressure was 230 systolic and 180 diastolic. The pulse rate was slow and regular. The apex beat was felt in the midclavicular line in the fifth interspace. There was no tortuosity or obvious thickening of the palpable arteries. No retinal lesions were seen but his pupils were small and the examination was incomplete. A concentration test had a volume of 600 c.c. with a specific gravity of 1.017. He was however taking a low salt diet. No quantitative determination of protein was made but the amount as judged from qualitative tests was small. The number of casts in twelve hours was 41,500 and all of them were hyaline casts. There were 34,000,000 white blood cells and epithelial cells, but there was a slight urethritis which accounted for this abnormality. The number of red blood cells per twelve hours was 1,680,000. Next day a timed specimen of day urine showed 46,000 casts and 969,000 red blood cells per twelve hours.

We are indebted to Dr. Wallace Wilson of Vancouver for the subsequent history and for the kidneys obtained at a partial postmortem examination.

During July, 1929, he began to suffer again from headaches. There was no change in the blood pressure levels and no definite alteration in the urinary abnormalities, and he still went on with his work.

On August 5, 1929, he felt well all day but in the evening he said he "did not feel just right" and lay down on his bed. A few minutes later he had a severe generalized convulsion which lasted for some time. When Dr. Wilson saw him he was relaxed but deeply unconscious with heavy stertorous breathing. The pulse rate varied between 130 and 140 and he was slightly cyanosed. About five minutes later he was dead.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were obtained at autopsy. They were of normal size measuring 12 × 5 × 4 cm. The capsule was somewhat adherent and stripped with difficulty, leaving a granular purplish red surface. The cut surface showed some reduction of the cortex and the arteries were definitely thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Many of the glomeruli are still fairly well preserved. Others, especially those lying in areas of scar development, show various degrees of fibrosis. In such areas many are reduced to small nodules of hyaline connective tissue. In those where the fibrosis is not complete there is a very definite increase in the number of nuclei in the tuft. These excessive cells are leucocytes, chiefly of the mononuclear type but also some of the polymorphonuclear. No exudative lesions are seen, however, such as the collection of fibrin or hemorrhage into Bowman's space.

Tubules. In the areas of the cortex which are comparatively free of scarring the convoluted tubules have preserved their normal shape and some are even larger than normal. The epithelium of most of these shows a very marked cloudy swelling and in places necrosis. In the areas of connective tissue development the tubules are distorted and compressed and their epithelium markedly atrophied. In the straight tubules of the medulla are many granular and hyaline casts.

Interstitial Tissue. Throughout the cortex there is an extensive irregular development of fibrous connective tissue. These scars are still quite cellular and scattered in them is an irregular and in places very dense infiltration with leucocytes, the majority of which are of the mononuclear type. This scar tissue has compressed and distorted the renal elements which it surrounds and where it reaches the free surface of the organ has produced slightly retracted scars.

Arteries. There is a very marked fibrous thickening of the arcuate arteries with proliferation of elastic tissue. The interlobular branches also show a marked thickening of their walls and the same sclerotic changes may be followed down to the smallest arteriolar branches and thus into the glomerular tufts.

SUMMARY

There is marked sclerosis of the larger arteries which extends down to the smaller branches of the glomeruli. In the extensive scars in the interstitial connective tissue as well as in some of the glomerular tufts there is a definite inflammatory infiltration of leucocytes. There is also present marked epithelial degeneration.

CASE LXII

Kenneth G. Aged thirty-nine.

Clinical Diagnosis. Arteriosclerotic Bright's disease with a superadded degenerative process.

Duration. Unknown. Observed during the last three years.

Etiology. Unknown.

Course. In 1913 one kidney became infected and was excised. In 1918 slight hypertension and albuminuria were noted. In 1922 the systolic pressure had risen to 250. When first seen in 1923 the blood pressure was still high but no symptoms other than slight dyspnea on exertion had developed. The urine showed no evidence of any active inflammation or degeneration and the amount of renal tissue was estimated as 91 per cent of the normal. In February 1926 signs of cardiac decompensation appeared. On July 5, 1926, consolidation developed at the base of the right lung with fever and leucocytosis. The edema increased and he died on August 18, 1926. Although there were large amounts of albumin in the urine and evidences of desquamation of renal cells, the blood urea concentration was not increased.

RELEVANT CLINICAL DETAILS

In 1913 he was in a railroad accident. His arm was crushed and had to be amputated. The wound suppurated and he had a prolonged fever. Pus was present in the urine and he suffered from renal colic until his left kidney was excised. He made a complete recovery.

In 1918 when he applied for service with the Red Cross his blood pressure was found to be 140 systolic and a little albumin was found in the urine.

In 1922 a chance examination revealed a systolic pressure of 250 and a trace of albumin in the urine.

In October 1923 he was seen for the first time. There were no symptoms except that he was aware that he could not do as much physical work as before but he attributed this to being rather out of condition. The pulse rate at rest was over 100 but was quite regular. The heart was enlarged to the left. The radial and brachial arteries were not noticably thickened. The systolic blood pressure was 220 systolic and 125 diastolic. There was very little increase in pulse pressure after exercise but his pulse rate accelerated markedly. A concentration test had a volume of 264 c.c. per twelve hours with a specific gravity of 1.029. The number of red blood cells was 49,500 per twelve hours, a number within the range of normal variation. There were 247,500 white blood cells and epithelial cells. The rate of protein excretion was 330 mg. per twelve hours. The number of casts was 14,600 of which 5 per cent were epithelial, 6 per cent granular and 89 per cent were hyaline. These results were regarded as excluding any active inflammation or degeneration. The ratio test showed that he had 91 per cent of the normal amount of renal tissue, a result which indicated that hypertrophy had compensated very well for the loss of renal tissue from pyonephrosis in 1913.

He was not seen again until 1926 on July 29. He stated that during this interval he had remained without obvious trouble until April 1926 when his feet became swollen and he had difficulty in breathing. In spite of energetic treatment his circulatory condition did not improve. On July 5 he was feverish and his doctor found signs of pulmonary consolidation. His condition had grown worse rather than better since then.

On July 30, 1926 he came to the hospital. There was heavy edema to the waist. His heart was fibrillating; the average blood pressure was still high. The lungs were congested and he was cyanosed, dyspneic and slightly irrational. The red blood cells numbered 6,390,000 per cubic millimeter. A concentration test had a volume of 254 c.c. and a specific gravity of 1.024. It had a deep mahogany color but, unlike the mahogany urine of the initial stages of glomerular nephritis, was perfectly clear. No red blood cells could be found but the number of white blood cells and epithelial cells was 4,180,000 per twelve hours. The rate of protein excretion was measured for nine successive days and was found to vary from 700 to 2130 mg. per twelve hours. The number of casts was 212,000 per twelve hours. Of these 15 per cent were epithelial, 10 per cent granular and 75 per cent were hyaline. It seemed then from these figures that an active degenerative process had been grafted on what had previously appeared as a simple renal arteriosclerosis. The blood urea concentration was 26 mg. per 100 c.c.

There was a transient decrease in edema at first but later the evidences of cardiac failure became more marked and the patient died on August 18, 1926.

PATHOLOGICAL OBSERVATIONS

One kidney, heart, spleen, left lung and a portion of liver only were available for postmortem examination.

The heart was about one and one-half times its normal size. The right ventricle and auricle were considerably dilated, and the left ventricle dilated and its wall moderately thickened. The valves were normal, but the coronary arteries showed many yellow spots in their intima. The heart muscle was normal.

The left lung was greatly congested and contained several hemorrhagic infarcts.

The spleen was small, measuring 10 × 4 × 3 cm., but except for a marked congestion was normal.

The piece of liver showed a marked cyanotic atrophy.

The one kidney was normal in size, measuring 13 × 7 × 5 cm. The capsule stripped easily leaving a smooth surface of normal color. The cut surface except for some opacity appeared normal. The renal arteries were definitely thickened and dilated.

MICROSCOPICAL EXAMINATION

Sections of lung show the alveoli filled with red blood cells. An artery is filled with partially organized thrombus.

Sections of the spleen and liver show nothing abnormal except the dilatation of the venous system, and sections of heart muscle are normal.

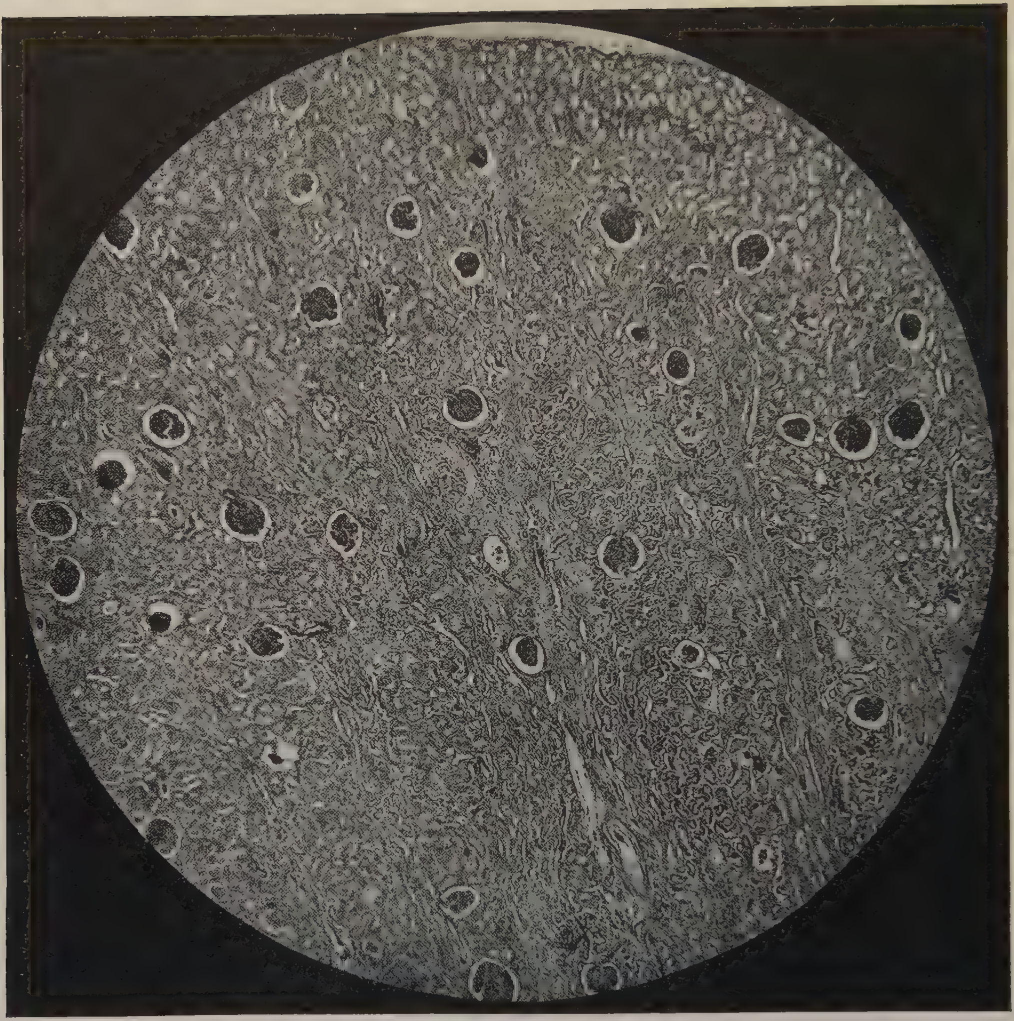

Plate LXII a

Many of the glomeruli are considerably increased in size. There is a diffuse rather extensive proliferation of connective tissue throughout the cortex so that in some regions the tubules show a moderate atrophy. Throughout the greater part of the section they preserve their normal structure.

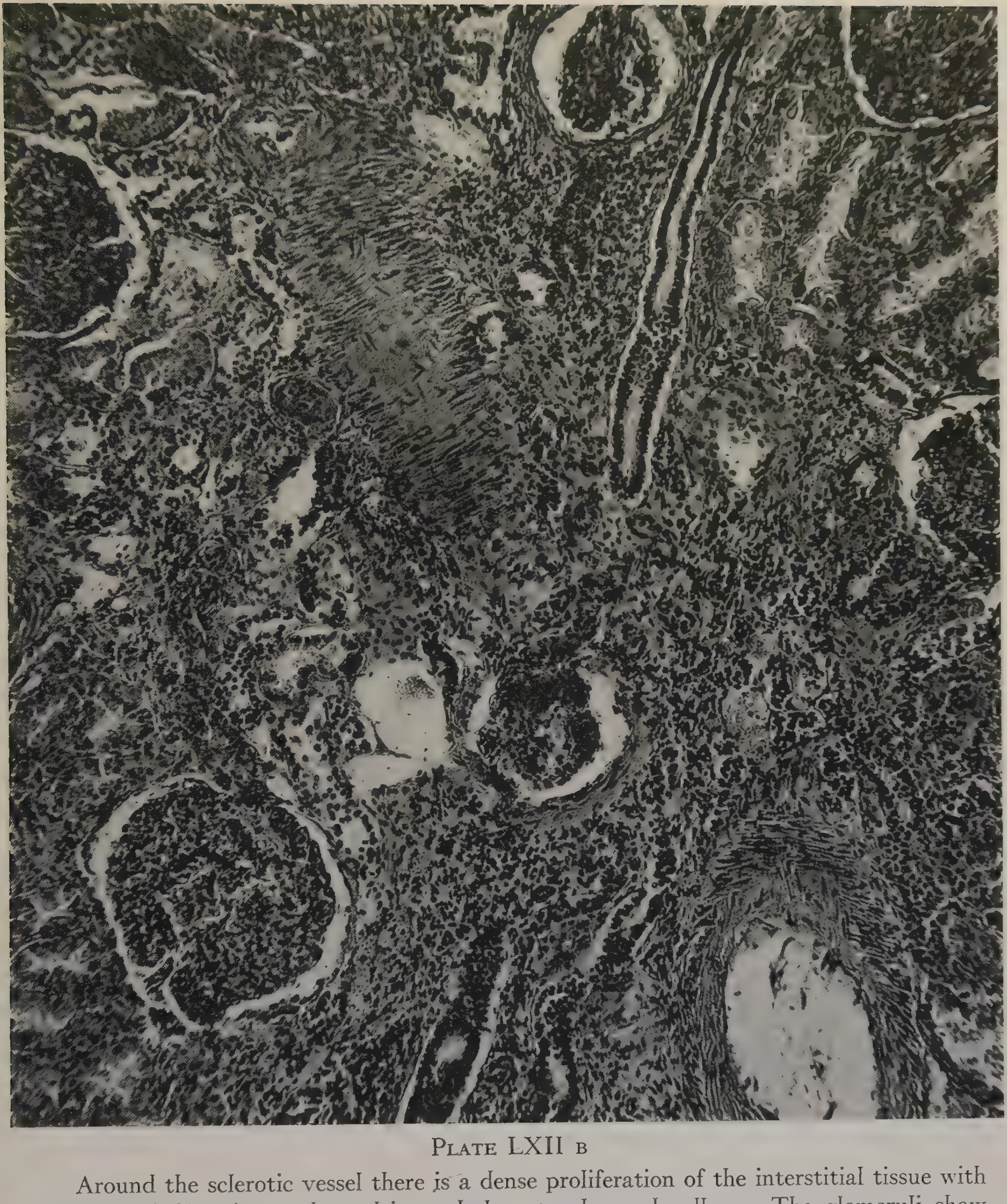

Plate LXII b

Around the sclerotic vessel there is a dense proliferation of the interstitial tissue with round cell infiltration and resulting tubular atrophy and collapse. The glomeruli show moderate involvement.

Kidney. *Glomeruli.* The glomeruli throughout the greater part of the cortex are practically normal. The capsular spaces are free, and there is no significant fibrosis around or in the tufts. In those regions of the cortex where there are fibrous scars the glomeruli show varying degrees of fibrosis. In some there is a just perceptible intracapillary thickening of the interstitial tissue while in others the whole tuft is transformed into a hyaline mass. The number of destroyed glomeruli is however small as compared to the total number.

Tubules. In the scars previously mentioned the convoluted tubules and broad limbs of Henle's loop are compressed and some show a considerable atrophy of their epithelium. In the free portions of the cortex the tubules are of normal size and shape. The epithelium in many, however, is swollen and granular and in patches there is a marked fatty degeneration. A moderate number of hyaline and granular casts are present. In the collecting tubules there are also casts, mostly hyaline. No free blood cells or blood casts are present.

Interstitial Tissue. Scattered throughout the cortex are areas of interstitial proliferation which form small fibrous scars with an accompanying atrophy of the parenchyma. In these scars there is a moderate round cell infiltration. There is no significant proliferation of the interstitial tissue of the medulla.

Arteries. There is a marked fibrous thickening of the intima of all of the arteries in the kidney. Both the larger arcuate vessels between the cortex and medulla and the small branches to the cortex are equally involved.

SUMMARY

The vessels of the kidney show a marked arteriosclerosis, a part of a general involvement of the arteries. In the kidney tissue there is an associated moderate fibrosis of the interstitial tissue with scar formation. Many glomeruli remain unaffected and there are recent degenerative changes in the tubular epithelium.

CASE LXIII

William G. Aged fifty-five.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Duration. Unknown. Observed during the last two days.

Etiology. Unknown.

Course. In 1914, eight years before his death, he was already aware of undue dyspoea on exertion but it was not until February 1921 that he began to suffer from anginal attacks at intervals of two or three months. By December 1921 obvious evidences of cardiac decompensation were present. He was seen on February 19, 1922. The legs were edematous and the bases of the lungs congested. The number of red blood cells was 4,100,000 per cubic millimeter. The heart was enlarged and its action irregular. The systolic pressure was 170 and the diastolic 120. The retinal vessels did not seem abnormal for a man of his age. Routine urine examinations showed that the urine contained considerable amounts of albumin. The blood urea concentration was 110 mg. per 100 c.c.

A twelve hours' specimen of urine had a very dark amber color. The volume was 515 c.c. and the specific gravity 1.023. The rate of protein excretion was 2500 mg. per twelve hours. The sediment contained a moderate number of casts, mostly hyaline but with some renal failure casts also. A diagnosis of renal arteriosclerosis was made. Three days later the patient died.

PATHOLOGICAL OBSERVATIONS

The kidneys alone were obtained at autopsy. They were somewhat smaller than normal, measuring 11 × 5 × 4 cm. The capsule stripped fairly easily, leaving a surface scattered with small irregular scars of reddish brown color. The cut surface showed fibrosis of the cortex. The arteries were distinctly thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. The majority of the glomeruli are still well preserved. Their tufts are normal in size and Bowman's space is clear. In the fibrous scars which are scattered through the cortex, however, the glomeruli are compressed and distorted, their tufts are atrophic and occasionally more or less fibrous. In none of them is there any round cell infiltration.

Tubules. Except in the scars previously mentioned the convoluted tubules and broad ascending limbs of Henle's loop are essentially normal. Occasionally groups are found with some cloudy swelling of their epithelium and whose lumens are filled with granular material. In the scars the tubules are compressed and their epithelium is atrophic.

Interstitial Tissue. Scattered throughout the cortex are areas of scarring where the interstitial tissue is increased in amount. The new tissue is quite fibrous and among the fibroblasts and collagen fibrils are many round cells. The interstitial tissue in the areas of the cortex that are free of scars is essentially normal.

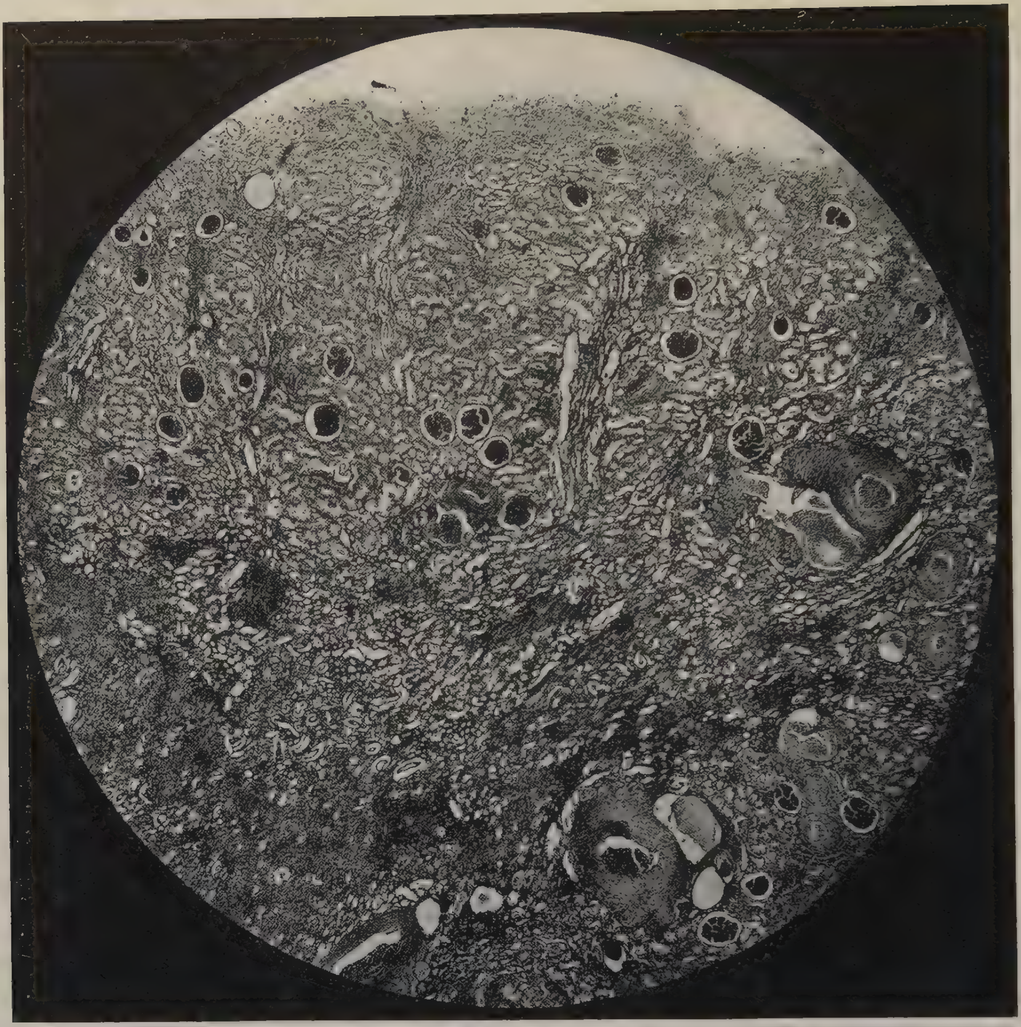

Plate LXIII a

Greatly thickened vessels of all sizes are seen throughout the section. There is a marked irregular thickening of the interstitial tissue which in many places is heavily infiltrated with leucocytes. Many glomeruli have preserved their normal size, others are atrophied and, judging from their irregular distribution, some have disappeared entirely. The tubules in the fibrosed areas, particularly along the surface of the organ, show varying degrees of atrophy. The surface of the kidney shows granulations.

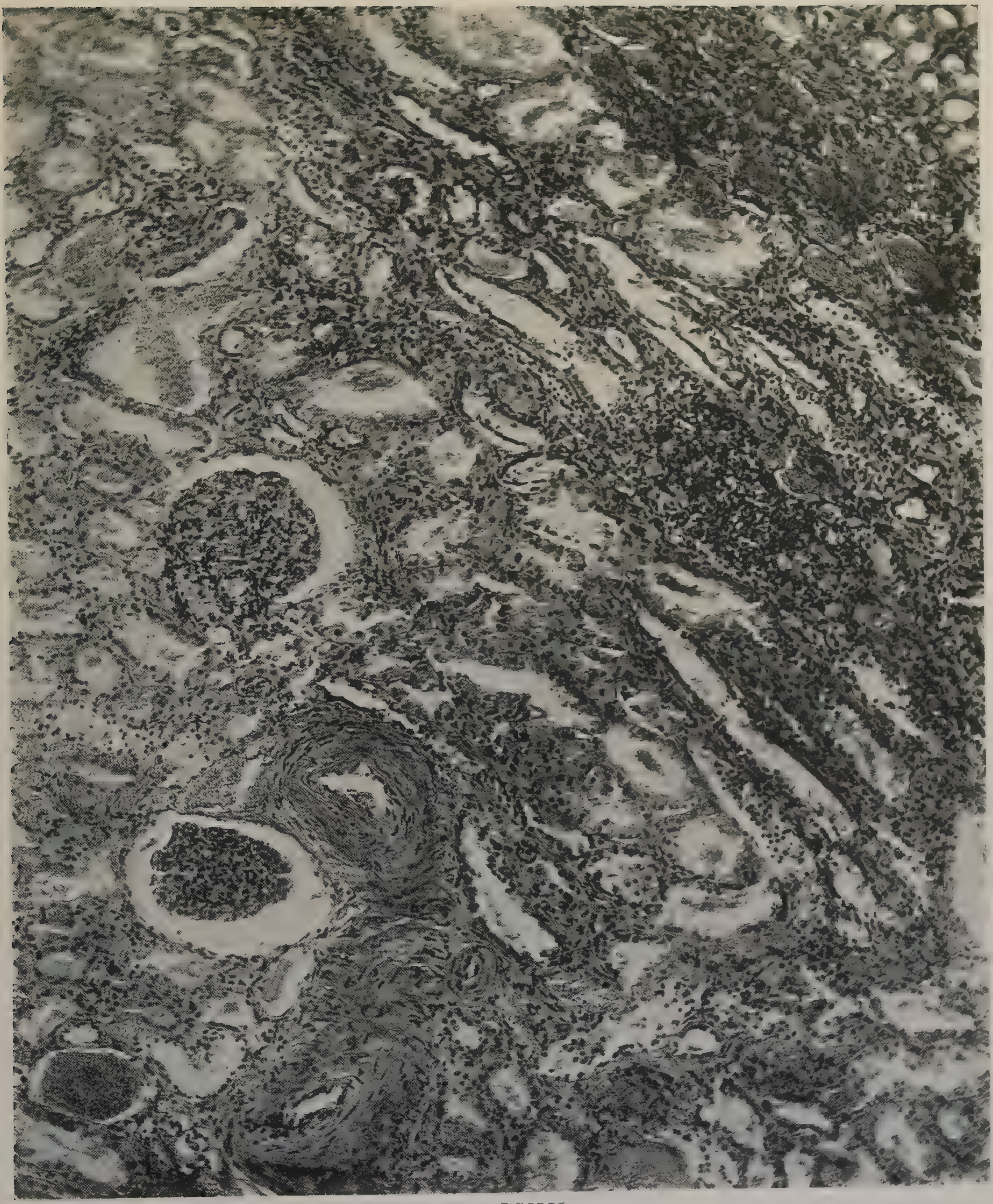

Plate LXIII b

The sclerotic arteriole is seen with irregular scarring and round cell infiltration in the interstitial tissue. There is some fibrosis of the glomerular tufts. The tubules show not only collapse but evidence of degenerative processes.

Arteries. There is a very marked fibrous thickening of the larger arcuate arteries. The interlobular branches to the cortex are also greatly thickened by fibrous tissue, but in most cases this lesion ends in the lower depths of the cortex so that the terminal arterioles to glomeruli are not involved.

SUMMARY

There is a marked arteriosclerosis of the large and medium sized arteries which has not extended into the terminal arterioles. Scars are present in the interstitial tissue. The glomeruli and tubules, except those included in the scars, are essentially normal.

CASE LXIV

John H. Aged eighty.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Etiology. Unknown.

Duration. Sixteen and one half years or more. Observed for last sixteen and one half years.

Course. In 1912 examination showed the presence of albumin and casts associated with hypertension, markedly thickened and tortuous arteries and an enlarged heart. In 1920 the amount of renal tissue was found to be 67 per cent of the normal but the sediment failed to show evidence of any active inflammatory or degenerative lesions. A diagnosis of renal arteriosclerosis was made. During the next eight years the urinary abnormalities remained constant but the amount of renal tissue decreased to 48 per cent of normal. He died of bronchopneumonia in 1928. The details of this case are incorporated in the general clinical discussion of arteriosclerotic Bright's disease.

PATHOLOGICAL OBSERVATIONS

At autopsy there was present a general arteriosclerosis with cardiac hypertrophy. The coronary, renal and cerebral arteries were especially involved. Healed apical tuberculosis with a fresh recrudescence in the pleura, an old healed aortic endocarditis, perisplenitis, chronic bronchitis and terminal bronchopneumonia were also found.

The kidneys were somewhat decreased in size, measuring 10 × 5 × 3 and 9 × 5 × 3 cm. The capsule stripped easily, leaving a finely granular red surface. The cut surface showed a fibrosis of the cortex and a moderate thickening of the arteries.

MICROSCOPICAL EXAMINATION

Glomeruli. The majority of the glomeruli are essentially normal. Their tufts are of normal size, the capillaries are patent and Bowman's space is clear. In those which lie near or are included in scars, however, the tuft is compressed or fibrous. Occasionally a completely hyalinized glomerulus is found. There is no leucocytic infiltration in or around these affected glomeruli.

Tubules. Except in the scars the tubules are well preserved. The epithelium of the convoluted tubules and broad ascending limbs of Henle's loop show a mild cloudy swelling and there is some granular material in the lumens of such tubules. In the scars the tubules are compressed, the degree of distortion depending on the amount of fibrous connective tissue around them. In such areas the epithelial cells are atrophic. There are a few hyaline casts in the lumens of the straight tubules.

Interstitial Tissue. The interstitial tissue in the greater part of the cortex is normal. There are, however, scattered areas where it is increased by a proliferation

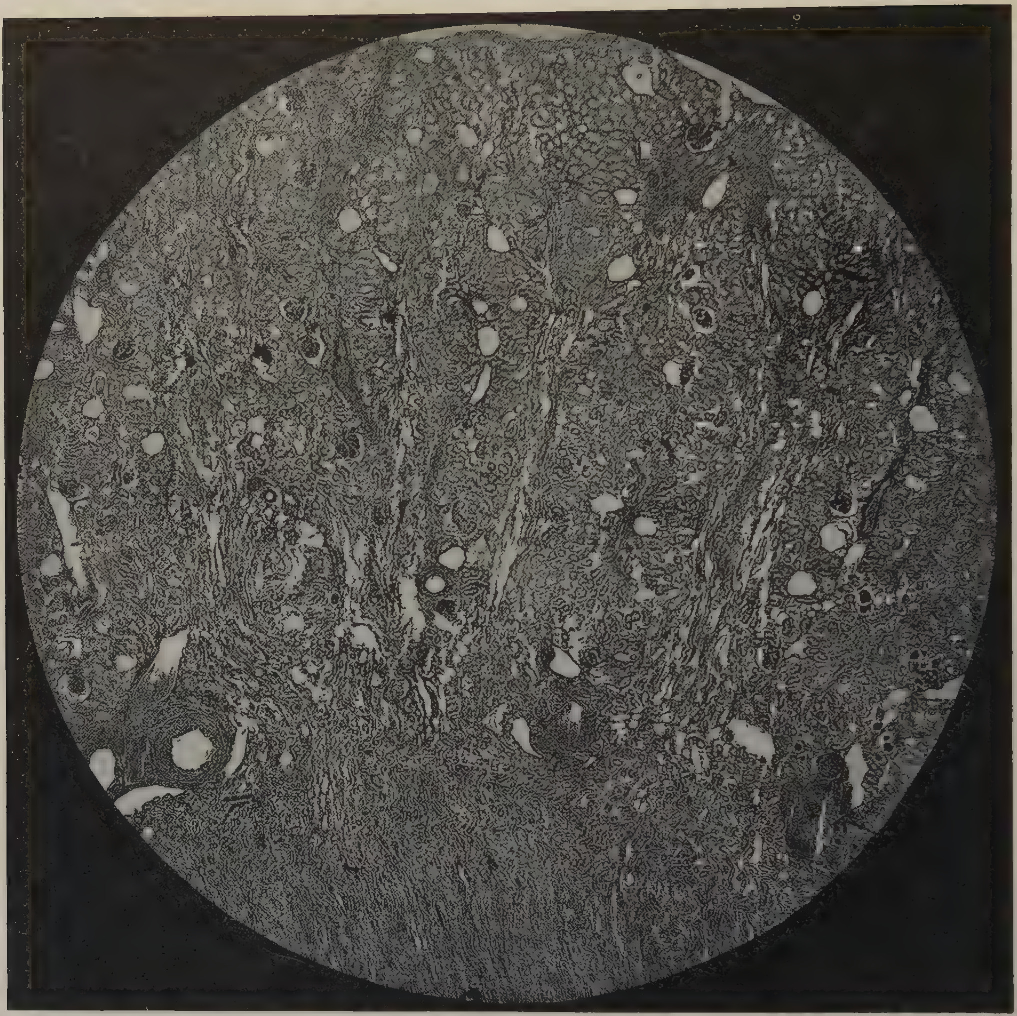

PLATE LXIV A

A large sclerotic artery and the thickened smaller branches are evident. There is a moderate scarring with some retraction and the formation of a granular surface. The tubules except in the areas of the scars are well preserved. The majority of the glomeruli also are not fibrosed. The numerous round holes seen throughout the cortex are glomerular spaces from which the tufts have fallen during the preparation of the section.

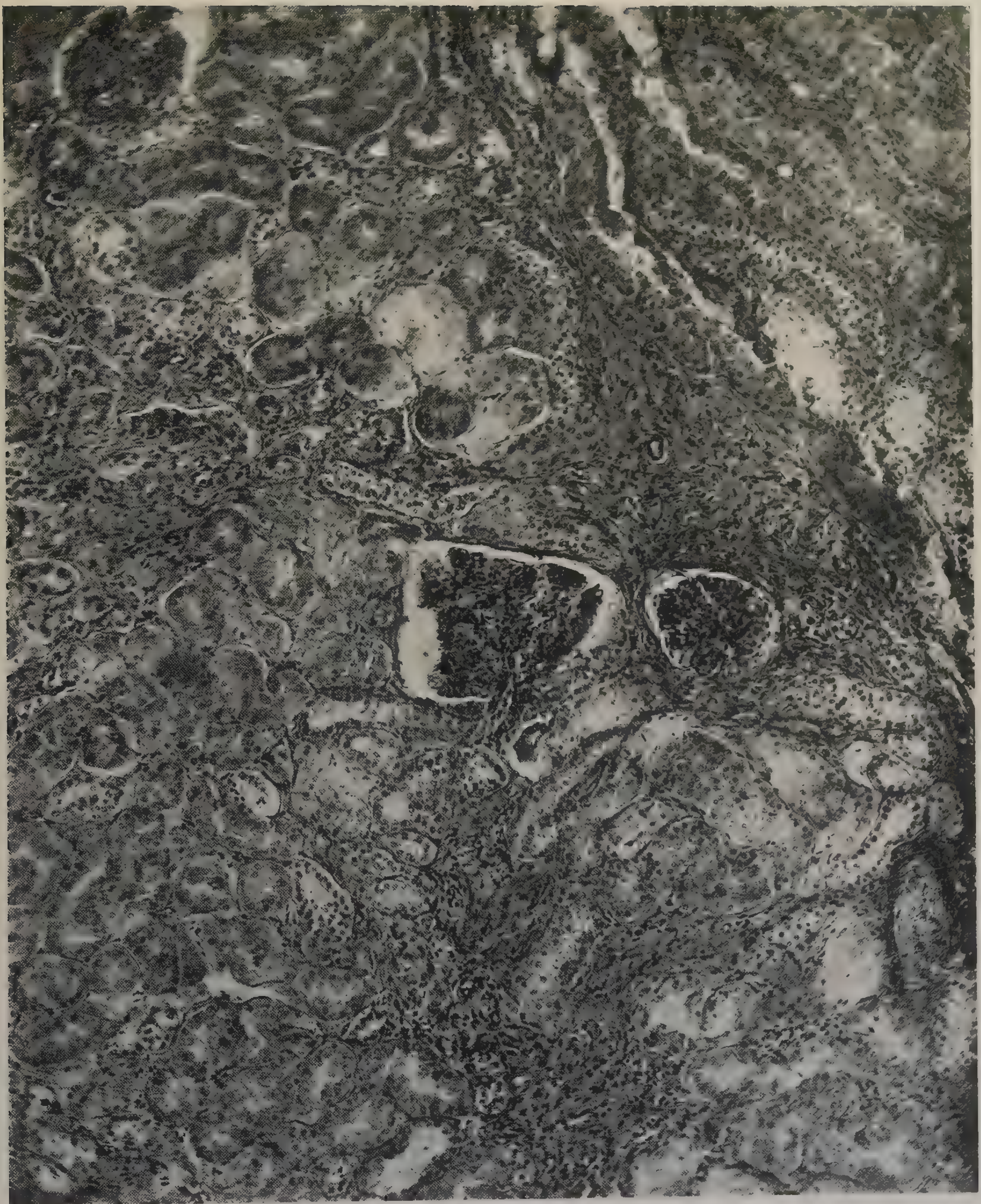

Plate LXIV b

A shrunken glomerulus is partially enclosed in scar tissue. There is marked cloudy swelling of the tubular epithelium.

of fibroblasts and collagen fibrils and by a cellular infiltration with round cells. Where these areas reach the free surface a retracted scar is formed.

Arteries. The large arcuate arteries show a marked fibrous thickening of their intima. The medium sized interlobular arteries are also thickened, but the arterioles to the glomeruli are not involved.

SUMMARY

There is a marked arteriosclerosis of the arcuate and the interlobular arteries. The smaller arterioles are normal. The tubules show mild degenerative lesions, and there is a moderate focal proliferation of the interstitial tissue.

CASE LXV

Martha H. Aged thirty-six.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Etiology. Toxemia of pregnancy?

Duration. Seven years. Observed during the last three years.

Course. In 1917 albuminuria and hypertension developed during pregnancy and the toxemia was allowed to continue for three and one-half months before a cesarian section was performed. When first seen in 1921 there was hypertension, retinal arteriosclerosis and signs of an aortic regurgitation. The urine contained only a trace of protein and the sediment gave no indication of any active inflammatory or degenerative process. It was estimated that 61 per cent of the normal amount of renal tissue was still functioning. In 1924 she died in a dehydrated state following a period of continued vomiting. The urine contained many renal failure casts and the blood urea concentration was 318 mg. per 100 c.c. on the day before she died.

RELEVANT CLINICAL DETAILS

In 1915 she had an attack of acute arthritis which apparently left no permanent injury. In 1916 she passed a life insurance examination and was told that her heart was normal. In 1917 when three months pregnant the urine which had previously been normal was found to contain albumin. She complained of headache, and edema of the legs developed soon afterwards. These symptoms progressed and when the sixth month of pregnancy was reached she became blind. Cesarian section was not done until two weeks later and she did not fully recover her sight until a month after the termination of pregnancy. She never fully recovered her strength and suffered especially from severe recurrent headaches and precordial pain and dyspnea on exertion.

When seen early in 1921 the heart was found to be greatly enlarged to the left and along the sternum a diastolic and systolic murmur could be heard. The blood pressure was 170 systolic and 108 diastolic. The retinal arteries were small and tortuous and the veins were full and pinched at the discs. A concentration test gave a volume of 369 c.c. per twelve hours, with a specific gravity of 1.021. The rate of protein excretion was 81 mg. per twelve hours. Hyaline casts were found and one or two epithelial and granular casts but the number of casts was not large. There was no evidence of any excess of red blood cells or of white blood or epithelial cells. The blood urea concentration was 21 mg. per 100 c.c. The urea ratio test showed that 61 per cent of the normal amount of renal tissue was still functioning.

During the next year the patient was seen on several occasions. There was no apparent change in her condition. She was easily tired, suffered from occasional severe headaches, and from precordial pain and dyspnea after any unusual exertion.

Late in 1924 she was brought to the hospital in a semiconscious state. Three weeks previously one of her headaches which usually passed off in twenty-four to

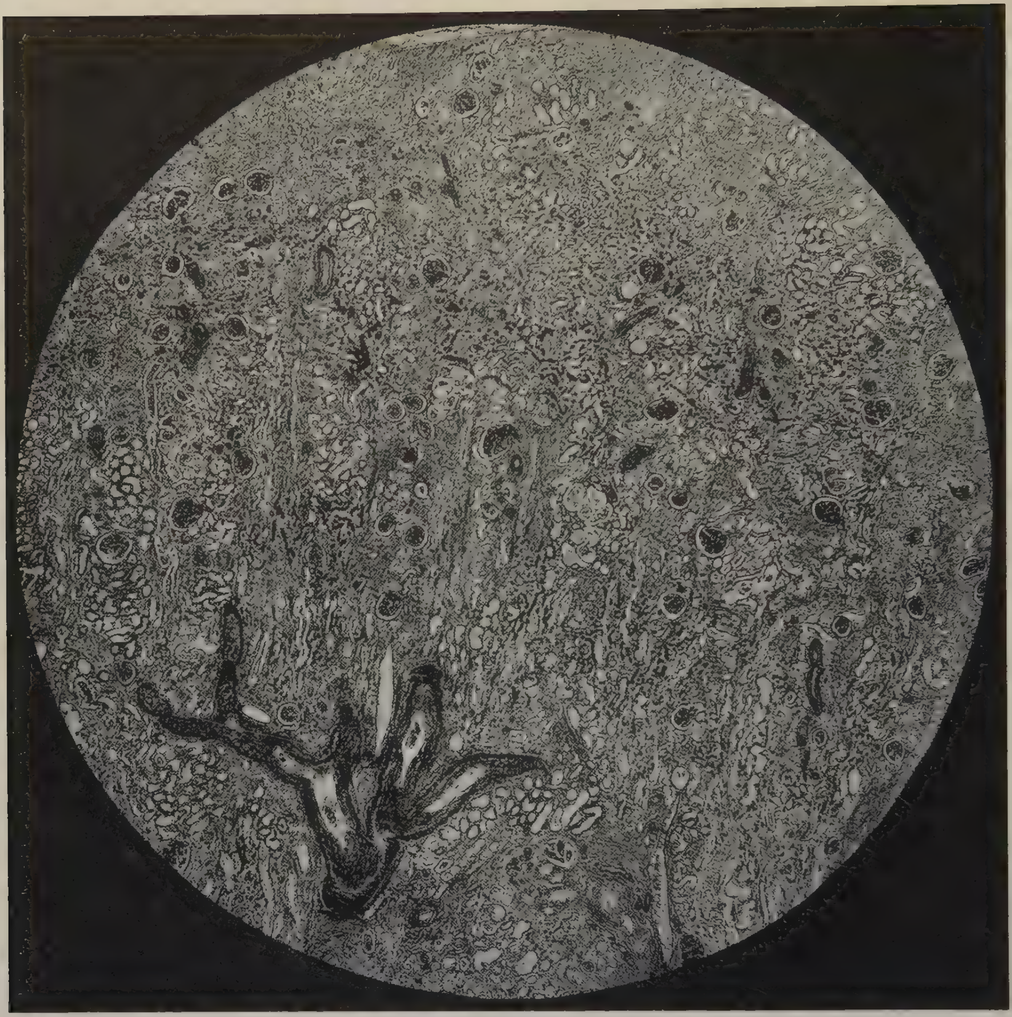

Plate LXV a

The extreme sclerosis of all the branches of the arteries both large and small, is plainly seen. There is extensive development of scar tissue throughout the cortex and as a result there is an irregular atrophy of the tubules. Some glomeruli are hypertrophied and many show varying degrees of obliteration. The granulation of the surface of the kidney may be seen.

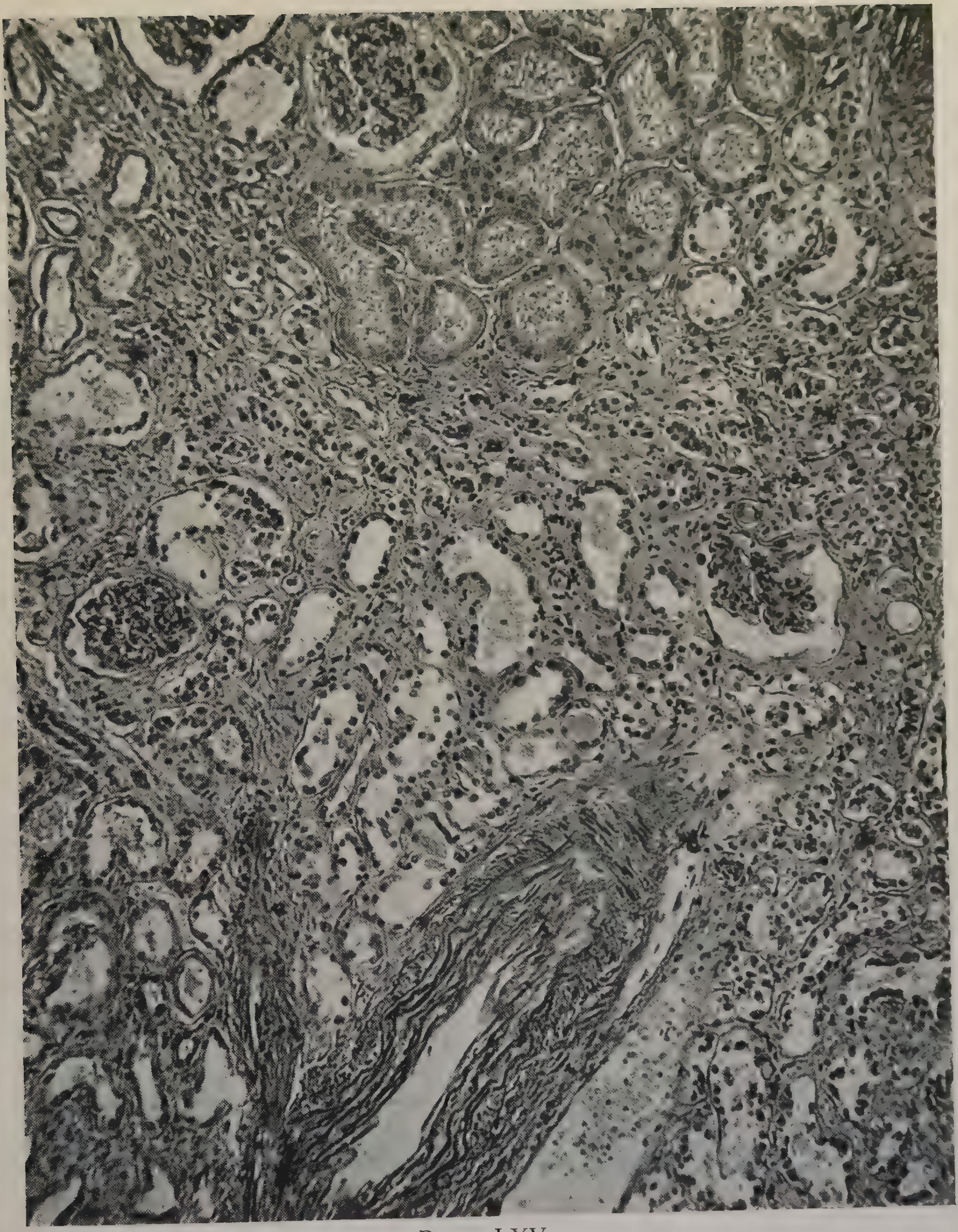

Plate LXV b

The hyperplastic form of elastic tissue proliferation is well seen in the artery. There is an irregular scarring of the interstitial tissue with areas of compensatory hypertrophy in the tubules. The epithelium of some of these shows a marked cloudy swelling. (Cf. Plates LXXX–LXXXIII, LXXXV.)

forty-eight hours had persisted in unusual intensity. It was accompanied by nausea and vomiting. She had been unable to eat or even to take water. Her weight fell from 115 lbs. to 89 lbs., and she passed into a stuporous condition with occasional twitching of the muscles. Examination showed no changes in the condition of the heart. The blood pressure was 240 systolic and 140 diastolic. The blood urea concentration was 318 mg. per 100 c.c. A specimen of urine obtained by catheter had a specific gravity of 1.017. The concentration of protein was 576 mg. per 100 c.c. The sediment contained a large number of renal failure casts. She died on the day following admission.

PATHOLOGICAL OBSERVATIONS

The heart was found greatly enlarged at autopsy, there being a marked hypertrophy of the left ventricle. On the aortic valve there was a mass of hard fibrous verrucous nodules which produced a stenosis and insufficiency. The lungs were congested, the spleen small and the arteries well preserved.

The kidneys were small; about two-thirds normal size. The capsules stripped with difficulty, leaving a congested purple irregular surface. On the cut surface the markings in the cortex were indistinct. The renal arteries were definitely thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. A considerable number of the glomeruli are practically normal. In others there is a varying amount of connective tissue proliferation varying from a just noticeable thickening between the capillary loops to a complete obliteration of the glomerular tuft. In many instances the fibrosis may be seen to originate in the wall of the afferent arteriole and to extend into the tuft. In some the resulting involvement of the tuft is slight, while in others practically the whole structure is transformed into a mass of fibrous tissue. Other glomeruli are one-half their normal diameter and in some the capsular space is dilated. In none, however, is there any leucocytic infiltration or inflammatory exudate.

Tubules. There is a marked irregularity in the size of the convoluted tubules in the cortex. In the regions of scarring to be described later, they are small and distorted with a low atrophic epithelium. Some of the tubules in these regions exist only as a solid compressed cord of atypical cells. Outside these areas the tubules are of normal size, or groups are found greatly enlarged and lined with a thick hypertrophied epithelium. In many of these cells there is marked evidence of degenerations of various types. The majority of the lumens are filled with granular material and in many definite hyaline or granular casts are present.

The straight tubules of the cortex are practically normal except that there are many casts, principally of the hyaline type in their lumens as well as large renal failure casts.

Interstitial Tissue. Throughout the cortex there is a heavy diffuse development of fibrous connective tissue which replaces a considerable part of the parenchyma.

Tubules and glomeruli are enclosed by it with a resulting compression, collapse and atrophy of them. The fibrous thickening is particularly marked about the arteries, and here and there are areas of moderately dense round cell infiltration. The interstitial tissue of the medulla is also increased in amount but the straight tubules are well preserved.

Arteries. All of the arteries show a severe sclerosis. There is a marked fibrous thickening of the intima of all the arteries, from the larger ones deep in the cortex to the smaller branches in the outer layers of it. There is also a marked hypertrophy and hyperplasia of the elastic tissue of the intima of these vessels. In some the lumen is almost completely obliterated. Not only are there proliferative lesions present inside the vessels, but there is also a considerable perivascular fibrosis, accompanied by a moderate round cell infiltration.

SUMMARY

The vessels of the kidney show an extreme arteriosclerosis extending into the smaller branches and destroying the glomerular tufts. A diffusely irregular and very extensive destruction of the parenchyma of the cortex by connective tissue proliferation is found. There is marked evidence of active degenerative processes in the epithelium.

CASE LXVI

William L. Aged forty-five.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Duration. Unknown. Observed during the last nine days.

Etiology. Unknown.

Course. The patient knew that in 1921 his systolic pressure had been 180 but he had no symptoms. In December 1925 he coughed up some blood. He consulted a doctor at that time who was unable to discover any reason for the hemoptysis but noted that the heart was greatly enlarged and that the systolic pressure was 220 and the diastolic 150. An ophthalmoscopic examination showed no retinal hemorrhages or exudate. After a week in bed the blood pressure had fallen to 180 systolic and 120 diastolic. The urine at this time contained only a trace of albumin. The phenolsulphonephthalein excretion was 45 per cent. There was no obvious anemia.

He was able to continue his practice until February 1926 when blurring of vision, dyspnea on exertion, headache and dizziness obliged him to rest. At this time his physician observed that the discs were edematous and that spots of exudate had appeared on the fundi. The heart was larger than before, the pulse was rapid, there was congestion of the lungs and a marked albuminuria with occasional renal failure casts.

He was seen between March 23 and 25, 1926. A concentration test had a volume of 235 c.c. per twelve hours with a specific gravity of 1.014. The rate of protein excretion was 830 mg. per twelve hours. The number of casts per twelve hours was 19,600 and of these 14 per cent were hyaline casts and 86 per cent were renal failure casts. There were 750,000 red blood cells and 10,000,000 white blood cells and epithelial cells. The blood urea concentration was 207 mg. per 100 c.c. There was no essential change in the physical status as described for February, except that he had grown weaker. During the next nine days his blood pressure fell from 210 systolic and 135 diastolic to 120 systolic and 70 diastolic. He died suddenly on March 31, 1926.

PATHOLOGICAL OBSERVATIONS

Autopsy showed a general arteriosclerosis of moderate degree with cardiac hypertrophy, an acute fibrinous pericarditis and a secondary anemia.

The kidneys were somewhat reduced in size, measuring 10 × 5 × 3 cm. The capsule was adherent and the surface dark red in color and showed many irregular scars. The cut surface showed some reduction of the cortex with indistinct markings and the renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. Practically all of the glomeruli show more or less fibrosis. The capillaries of the tuft are thickened and in many instances the fibrosis is of such extent as to compress and obliterate the vessels. In some this fibrosis transforms the whole tuft into a fibrous hyaline mass. The thickening of the vessel wall can be also seen in the afferent arteriole, both before and just at its point of entry into the tuft. No leucocytic infiltration of any of the tufts can be found. Bowman's space contains some granular material in a few cases but in most of the glomeruli it is free.

Tubules. The majority of the convoluted tubules of the cortex are compressed and distorted by the developing interstitial tissue. Their epithelium is atrophied and irregular in shape. Other tubules are greatly dilated and contain colloid hyaline material. In the regions where the connective tissue proliferation is less marked the tubules are normal and some are even hypertrophied. In scattered areas marked cloudy swelling is present, with necrosis and desquamation. There are moderate numbers of granular and hyaline casts in the lumens of the tubules and in the collecting tubules are many large renal failure casts. No red blood cells or blood casts are found.

Interstitial Tissue. Throughout the cortex there is a diffuse proliferation of the interstitial tissue. The tissue is quite fibrous and though round cells may be found scattered among the collagen fibrils, no large accumulations of dense infiltration are present, nor can polymorphonuclears be found. Retraction of this tissue where it reaches the free surface has produced irregular scars.

Arteries. All of the arterial tree shows a fibrous thickening, from the large arcuate arteries through the interlobular arteries and afferent arterioles to the capillaries of the tuft. The process is almost a pure fibrosis, very few round cells being present within the artery wall or around the vessel.

SUMMARY

There is a very marked arteriosclerosis of the entire arterial tree down to and including the capillaries of the glomeruli. The glomeruli are severely affected, and the interstitial tissue is thickened with fibrous tissue. The epithelium shows mild recent degenerative lesions. Renal failure casts are present.

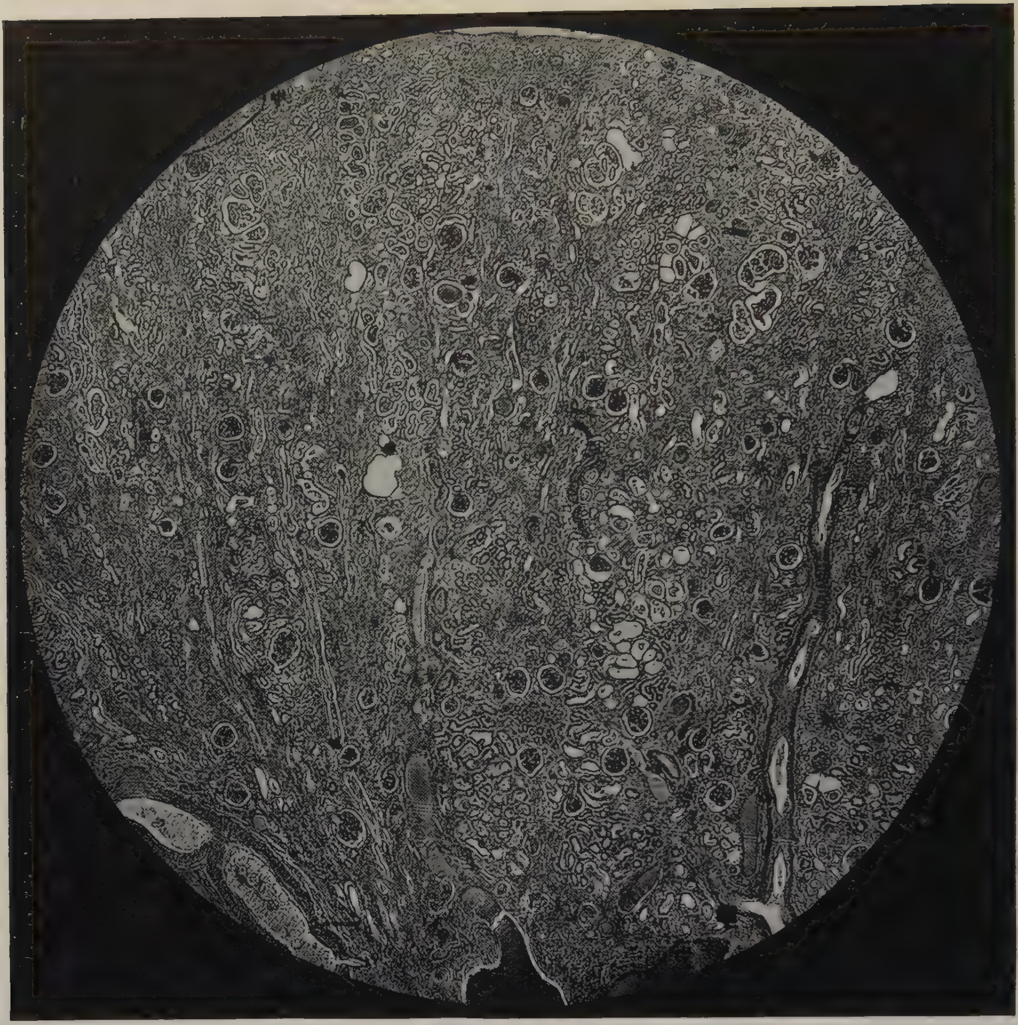

PLATE LXVI A

The arteries of the cortex show an extreme fibrous thickening. There is a marked increase in the fibrous connective tissue of the kidney framework with resulting atrophy of the tubules in some places and cystic dilatation of them in others. These dilated tubules contain colloid. Some glomeruli are enlarged, others are fibrosed.

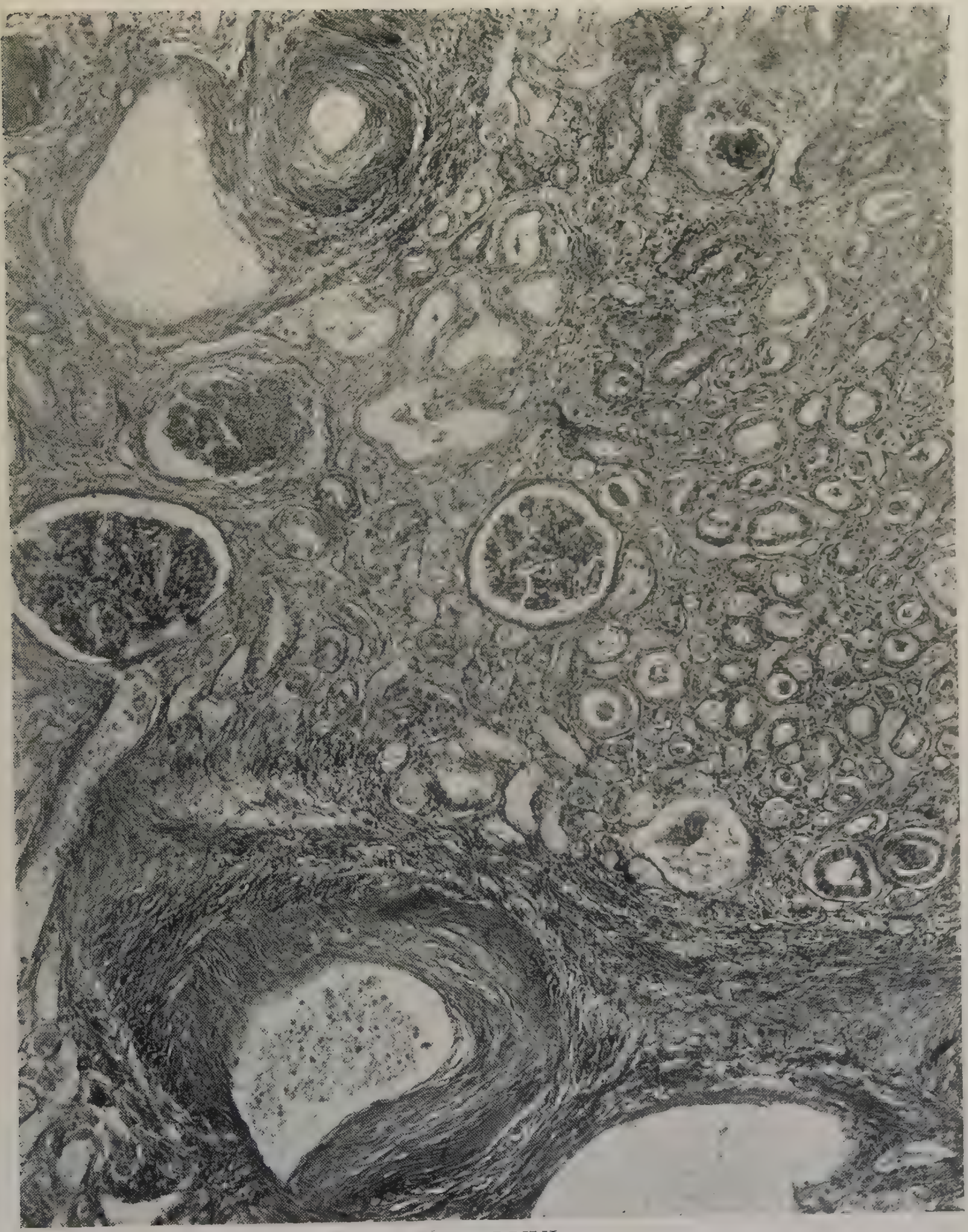

Plate LXVI b

The sclerosis of the arteries is extreme. The glomerular tufts show various stages of fibrosis. There is a diffuse fibrosis of the interstitial tissue with consequent deformity of the tubules. (Cf. Plates lxxxvi, lxxxvii.)

CASE LXVII

Jane M. Aged forty-five.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Etiology. Pregnancy toxemia?

Duration. Unknown. Observed for three years.

Course. In 1902 during pregnancy there was a long-continued toxemia which terminated with convulsions. In 1915 a routine examination showed a blood pressure within the limits of normal variation. No examinations were made therafter until May 1921 when the blood pressure was found to be 210 systolic and 140 diastolic. The urine contained almost no protein, 15,200 hyaline casts, no red blood cells and 350,000 white blood cells and epithelial cells per twelve hours. She was in fairly good health thereafter until May 1924 when she became first mentally confused, then stuporous and finally deeply unconscious. She died three days later. The blood urea concentration on the day before death was 98 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

In 1902, while pregnant, albumin was found in the urine. The amount increased and she was kept in bed for several months on a low diet. No blood pressure measurements were made. She finally became unconscious and was later told that she had severe convulsions. The pregnancy was terminated, but she had a prolonged convalescence because of a deep abscess which developed at the place where salt solution had been injected.

Between 1902 and 1915 she had three attacks of fever, pain in the left side and pyuria. In 1915 during the last attack her blood pressure was taken for the first time and was said to be normal.

In 1921 she began to suffer from headache, and dizziness, and came for examination. The heart was enlarged to the left, the peripheral arteries thickened and tortuous, the systolic blood pressure 210 and the diastolic 140. The concentration test had a volume of 175 c.c. per twelve hours with a specific gravity of 1.035. There was a trace of albumin and only a relatively small number of hyaline casts could be found. The blood urea concentration was 15 mg. per 100 c.c. The ratio test showed that 73 per cent of the normal amount of renal tissue was still functioning.

During the next three years she was seen on several occasions. The systolic pressure varied between 250 and 270 and the diastolic between 140 and 150. In spite of this constantly high pressure level she was practically free from symptoms except that she was at times conscious of a throbbing in her head. She was able to continue her work without interruption.

In June 1923 the concentration test volume was 385 c.c. per twelve hours with a specific gravity of 1.027. There was only a faint trace of albumin. In twelve hours, 15,200 casts were excreted. They were all hyaline. No red blood cells were found. The number of white blood cells and epithelial cells in twelve hours was 353,000. The ratio test showed that at this time 66 per cent of the normal amount of renal tissue was still functioning.

On May 18, 1924, she went to meet some people at a hotel but on the way became confused and forgot where she was going. She came home complaining of dizziness and went at once to bed. Next morning she did not seem to know where she was though she would answer questions. As the day advanced she became more stuporous and hard to rouse until at last she was quite unconscious, but when examined no evidence of paresis could be obtained. The blood urea concentration was 98 mg. per 100 c.c. The blood pressure was 270 systolic and 145 diastolic. The spinal fluid pressure was 220 mm. of water. She died next day without recovering consciousness.

PATHOLOGICAL OBSERVATIONS

Autopsy showed a general arteriosclerosis, the cerebral vessels being particularly involved. The heart was about one-half its normal size and the valves were normal. In the right hemisphere of the cerebellum was a recent hemorrhage 5 cm. in diameter which extended over 1.5 cm. into the left hemisphere.

The kidneys were somewhat small, measuring 12 × 4.5 × 3 cm. The capsules stripped easily leaving a fairly smooth surface and the markings on the cut surfaces were normal. The left renal artery was distinctly thickened. Otherwise, except for a beginning bronchopneumonia the organs showed no significant gross lesions.

MICROSCOPICAL EXAMINATION

Glomeruli. The great majority of the glomeruli are practically normal. A few show a slight or moderate increase in intracapillary connective tissue and occasionally a completely hyaline tuft is seen. There is no significant decrease in their number, however, nor any hypertrophy or dilatation of them.

Tubules. The convoluted tubules of the cortex are also essentially normal, except in the regions of scarring described later. Here there is more or less atrophy of the tubules and their cells depending on the amount of increase in the interstitial connective tissue, and occasionally cloudy swelling may be found.

The straight tubules of the medulla are also normal. A few contain granular material and after considerable search a few hyaline casts can be found.

Interstitial Tissue. Scattered through the cortex are small scars, consisting of fibrous connective tissue. These are not extensive and only a few tubules or a single glomerulus are surrounded by each so that no appreciable amount of the cortical tissue is involved. There is only a moderate round cell infiltration in these scars.

Arteries. All of the arteries show a moderate sclerosis. There is a definite fibrous thickening of the intima of all of them, even the finer branches to the periphery of the cortex. About the larger arcuate branches in the deeper portions of the cortex there is considerable perivascular connective tissue proliferation and some round cell infiltration.

SUMMARY

The arteries of the kidney show a moderately severe arteriosclerosis, a part of the general arterial disease, but there is only a moderate associated damage to the renal tissue. Only slight evidence of active inflammatory or degenerative processes are seen.

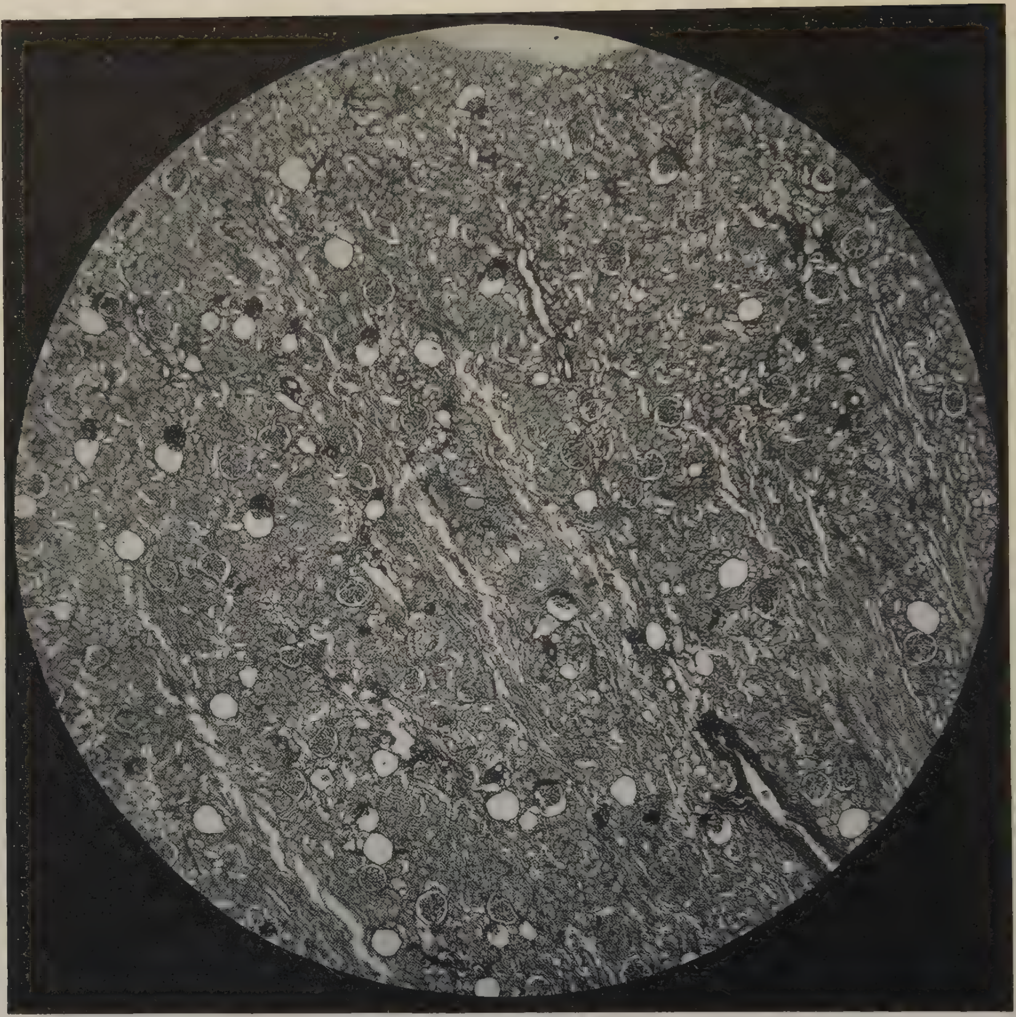

Plate LXVII a

The thickened renal arteries are evident. There is a diffuse moderate increase in the interstitial connective tissue with round cell infiltration in some places. The tubules are not particularly deranged and most of the glomeruli are essentially normal.

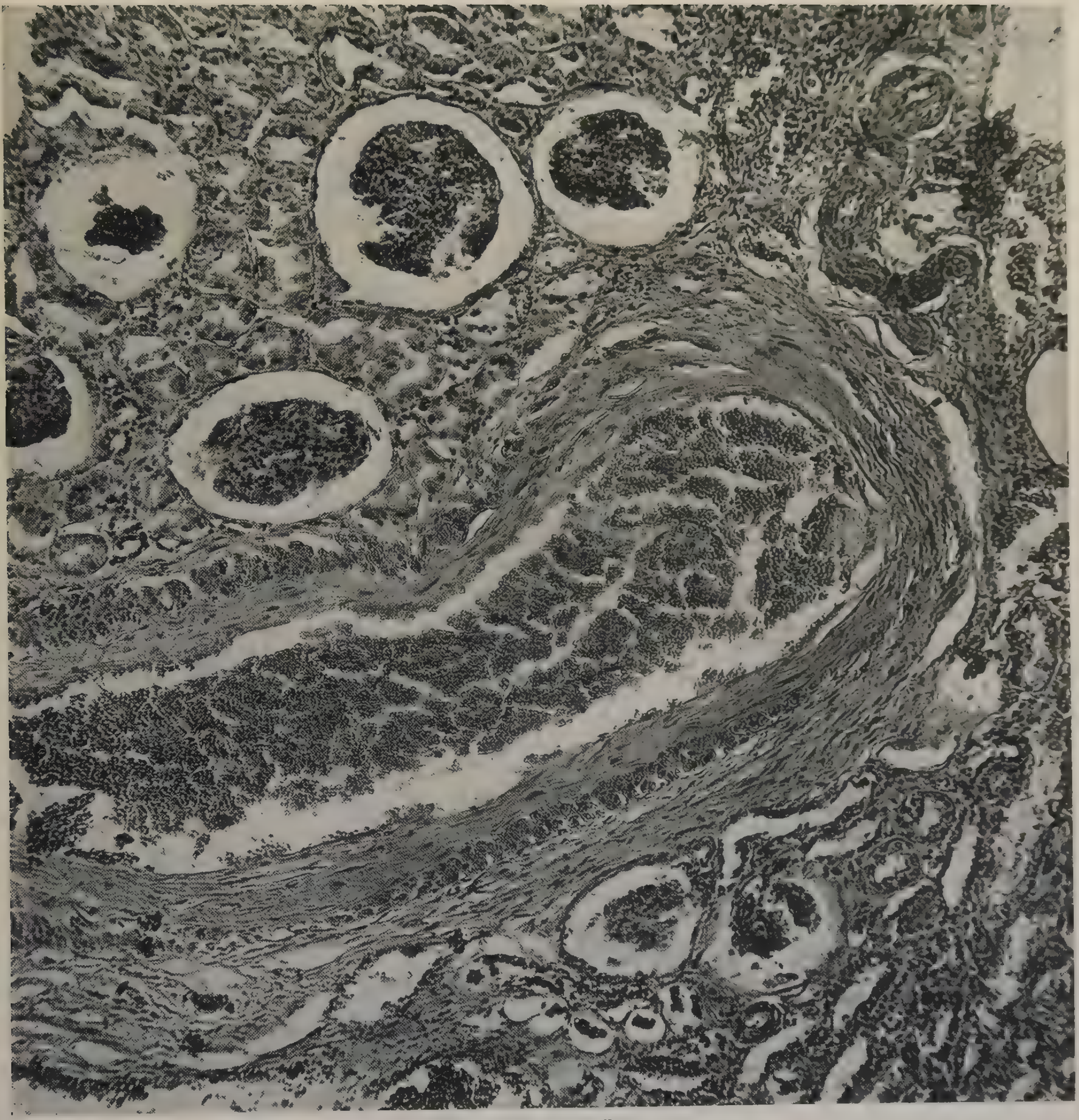

PLATE LXVII B

A greatly thickened artery is seen. The glomeruli are somewhat distorted by the development of connective tissue in their tufts. There is a moderate degeneration in the tubular epithelium.

Case LXVIII

Edward P. Aged fifty-seven.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Duration. Unknown.

Etiology. Unknown.

Course. In November 1923 the patient began to suffer from increasing dyspnea on exertion followed by edema of the legs. He was found to have a marked hypertension and cardiac decompensation. On three sucessive occasions his breathlessness and edema were relieved, but the fourth decompensation proved fatal, one year after the onset of symptoms. He was observed several times during 1924 and the results seemed to warrant the diagnosis of renal arteriosclerosis complicated at times by venous congestion.

RELEVANT CLINICAL DETAILS

This patient had a marked hypertension of unknown duration. At the age of fifty-six his heart began to fail. The first examination on April 30, 1924, was made after he had been nearly freed from his edema, the second in June after recovery from another decompensation, while the last three, carried out during October, November and December, were made over a period when all therapeutic measures had failed to rid him of edema and his heart was slowly failing. He died on December 11, 1924.

Table XXXVII
Rates of Excretion for 12 Hours

Date	Casts	R.B.C.	W. & Ep. C.	Protein, mg.	Blood urea, mg. per 100 c.c.
Apr. 30	126,600	0	460,000	210	40
June 4	213,000	520,000	780,000	670	
Oct. 18	550,000	2,000,000	3,550,000	500	
Nov. 5	295,000	746,000	1,080,000	370	78
Dec. 5	222,000	9,141,000	18,800,000	340	64

The observations made during April and June were entirely consistent with a diagnosis of renal arteriosclerosis. But during his last illness there was in addition a very definite increase in the number of red blood cells. In my experience this is unusual in cardiac decompensation but yet it seemed reasonable to associate it with a venous congestion in the kidney consequent on the cardiac failure.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found an arteriosclerosis of the aorta and of the coronaries with scars in the heart muscle, an incipient cirrhosis, apical healed pulmonary tuberculosis, chronic adhesive pleurisy and perisplenitis. As terminal infections there was also present a fibrinous pleurisy, acute colitis and bronchopneumonia.

The kidneys were reduced in size, averaging 11 × 5 × 4 cm. The capsule was somewhat adherent to the reddish purple granular surface of the kidney. The cut surface showed some narrowing of the cortex. The arteries were definitely thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. About one-half the glomeruli are fairly well preserved, their tufts being normal in size and showing no fibrosis and patent capillaries. The remaining glomeruli show various stages of fibrosis, most of them being transformed into hyaline fibrous masses. Among the fibrous tissues are a moderate number of leucocytes, the majority being mononuclears but polymorphonuclears may also be found. No exudate or red blood cells are found in Bowman's space.

Tubules. The convoluted tubules of the cortex are markedly distorted and deformed by the developing scar tissue. They are irregular in shape and compressed, often with no visible lumen, and are lined or filled with atrophic epithelial cells. In those portions of the cortex which are free of connective tissue, the tubules are of normal size and some are even hypertrophied. Their epithelium shows a recent mild cloudy swelling, and the lumens are filled with granular material and desquamated cells. There are a moderate number of hyaline and granular casts in the straight tubules.

Interstitial Tissue. About one-half the cortical tissue is replaced by fibrous scar which leaves free areas where the tubules and glomeruli are essentially normal. The scars are quite cellular and in places heavily infiltrated with round cells. Occasional polymorphonuclear leucocytes can also be found scattered among these leucocytes. In or near the scars the arterial lesions are especially marked, and where the scar reaches the free surface retracted areas are present.

Arteries. The larger arcuate arteries show a marked fibrous thickening of their intima and many of the interlobular branches passing up into the cortex are almost obliterated by the cellular fibrous proliferation of their intima. The finer arterioles to the glomeruli except in the areas of dense scarring are less involved and in many cases are normal in appearance.

SUMMARY

The larger and interlobular arteries show a severe sclerosis. There is extensive scarring of the cortex with atrophy of the enclosed glomeruli and tubules and inflammatory leucocytic infiltration. There is a recent parenchymatous degeneration of the epithelium of the convoluted tubules.

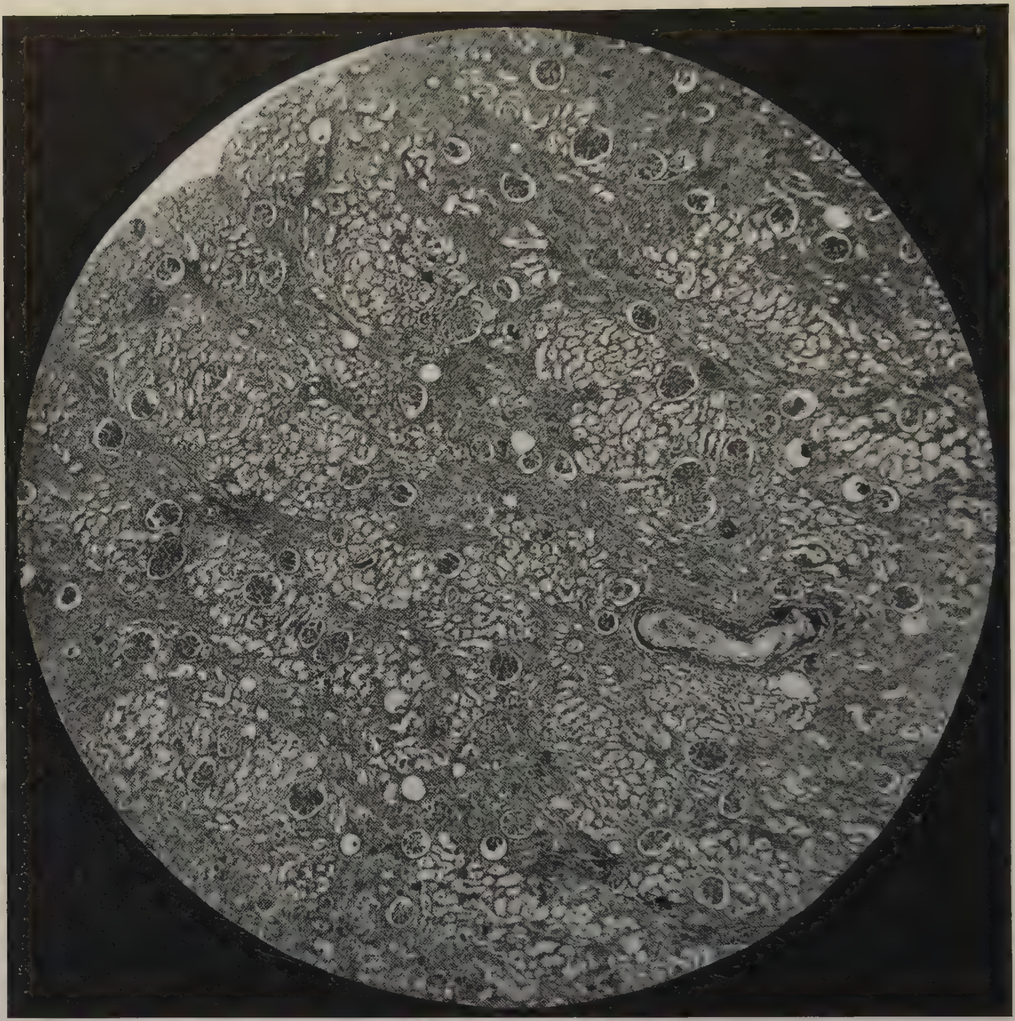

PLATE LXVIII A

A markedly sclerosed vessel is plainly seen. Throughout the cortex there is an irregular extensive development of scar tissue. In these regions there is marked atrophy of the tubules and fibrosis of the glomeruli. In the free areas both the tubules and glomeruli are hypertrophied. As a result of alternating retraction and proliferation of the tissues the surface is very granular.

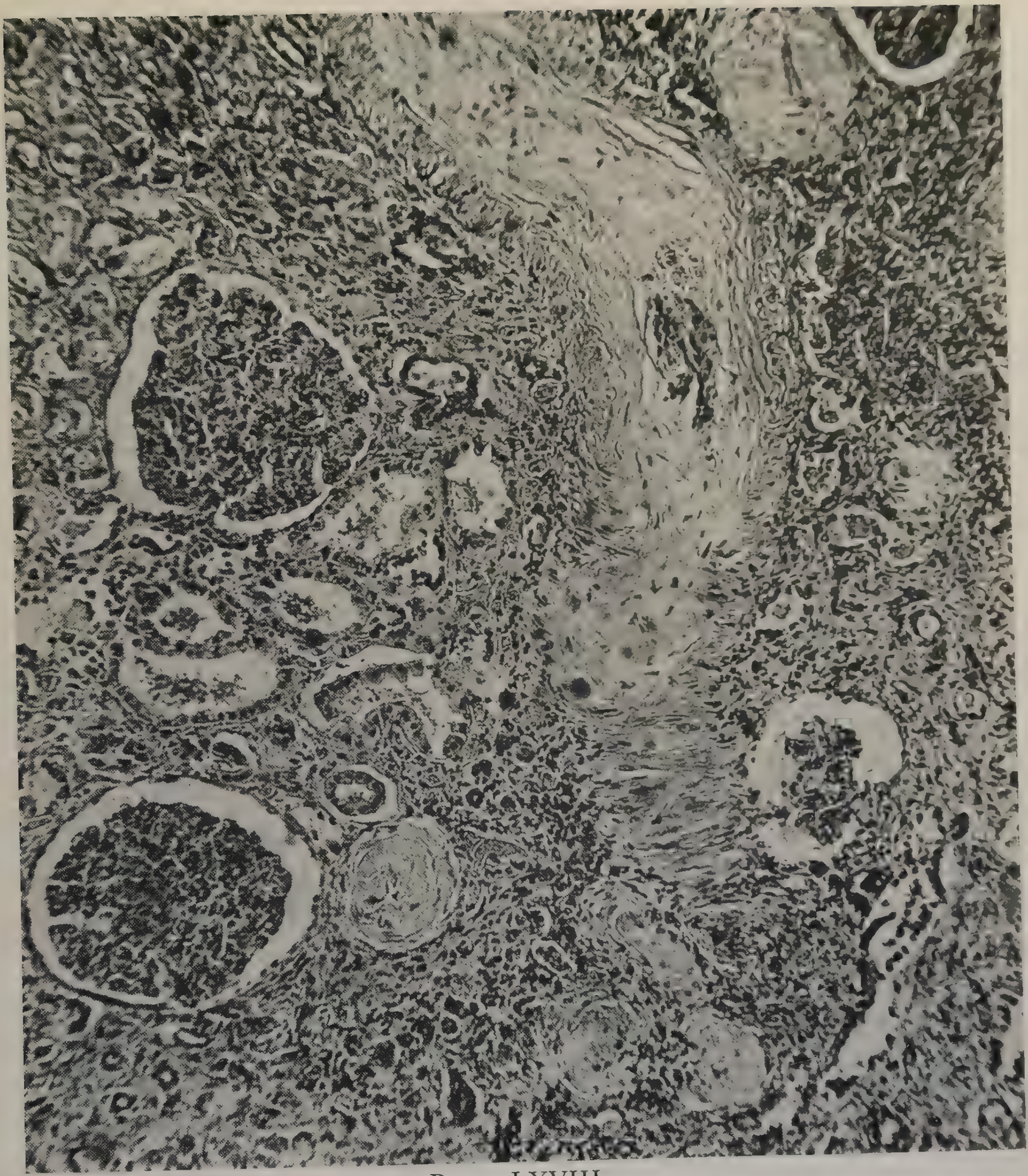

PLATE LXVIII B

A markedly sclerotic artery is shown with several hyaline glomeruli. In the two larger glomeruli there is a definite increase in nuclei of leucocytes and throughout the interstitial tissue is a diffuse round cell infiltration. Extreme tubular degeneration is also present. The details of the cellular elements in the glomeruli may be seen in Plate LXXXIV.

CASE LXIX

Tod P. Aged forty-nine.

Clinical Diagnosis. Arteriosclerotic Bright's disease with a superadded degenerative process.

Duration. Unknown. Observed for the last nineteen months.

Etiology. Unknown.

Course. Hypertension, though without symptoms, was known to have existed for several years before February 1925 when he developed signs of consolidation at the base of the left lung. Evidence of congestion of the lung persisted and there were occasional slight fever and hemoptysis. In March the urine contained a large amount of albumin, although there had previously been only a trace, and the sediment indicated the existence of an active degenerative process. During August 1925 an edema developed which involved his face and arms as well as his legs. Although the degree of edema varied, the nature of the renal lesion remained constant until death which came from cardiac decompensation in August 1926. At no time was the level of blood urea concentration above normal.

RELEVANT CLINICAL DETAILS

This patient was a hard working, rather hard living business man who knew that his blood pressure had been high for an indefinite number of years, but had not been aware of any symptoms. On February 15, 1925, he had repeated hemoptysis and became cyanosed and dyspneic. The systolic pressure which had been over 200 decreased to 170 but the diastolic pressure remained between 120 and 130.

He was seen for the first time on March 12, 1925. The pulse was rapid but regular, the heart enlarged, the blood pressure 170 systolic and 130 diastolic. The retinal arteries were narrow and tortuous. At the base of the left lung moist râles were heard and there was an area over which the percussion sound was impaired.

The rate of protein excretion averaged 1610 mg. per twelve hours during March, although in February the urine had contained only small amounts of albumin. The urine obtained after abstention from fluids had an average specific gravity of 1.026. It was perfectly clear but had a remarkably deep mahogany color and the plasma also was colored brown. This pigment was neither bilirubin nor urobilin. There were 580,000 casts of which 2 per cent were epithelial, 2 per cent granular and the remainder hyaline. A considerable proportion of the casts contained fat droplets. There were 3,600,000 red blood cells and 3,700,000 white blood cells and epithelial cells, many of which contained large granules or fat droplets. The blood urea concentration was 43 mg. per 100 c.c.

During the next year many sediment examinations gave essentially similar results. The routine urine examinations made before March 1925 had all shown only traces of albumin, occasional hyaline casts, and few cells, in other words a picture which excluded any very active inflammatory or degenerative lesion and one in consonance with the diagnosis of renal arteriosclerosis. It seemed, therefore, that an active degenerative process had involved an arteriosclerotic kidney. The slight increase in the number of the red blood cells was attributed to renal congestion.

Although the patient rested and although the diastolic pressure ultimately fell to about 90 there was a slowly increasing degree of cardiac disability. During August, when dietetic restrictions were neglected, an edema of the legs developed which extended to the face and arms. Although this edema in large measure disappeared later, his legs remained swollen. In April 1926 there was marked congestion of the lungs with recurrent hemoptysis. Thereafter his heart slowly failed. He died in August 1926. The blood urea concentration never exceeded 43 mg. and was once as low as 17 mg. per 100 c.c., although no determinations were made during the last few months of his life. Table XXXVIII gives counts made during the period when signs of cardiac failure were observed.

TABLE XXXVIII

Date	Number of casts in 12 hrs.	Differential (per cent)							R.B.C. 12 hrs.	W. & Ep. 12 hrs.	Protein, mg. 12 hrs.	Vol. sp. gr.	Blood urea
		BL.	EP.	GR.	FA.	W.	HY.	Broad					
1925 March 18	613,000	0	0	0	0	0	100	0	1,580,000	2,130,000	1,460	275 1.031	43
April 7	835,000	0	4	1	0	0	95	0	4,250,000	5,600,000	2,440	672 1.022	
May 22	137,000	0	0	0	0	0	100	0	6,350,000	15,900,000	1,030	635 1.011	
June 25	454,000	0	0	2	0	0	98	0	1,485,000	1,930,000	1,532	495 1.013	
Aug. 5	566,000	0	0	0	0	0	100	0	1,880,000	2,200,000	1,550	246 1.023	
Oct. 4	1,490,000	0	0	0	0	0	100	0	2,000,000	12,800,000	1,189	367 1.015	17
Nov. 13	15,200	0	0	0	0	0	100	0	28,500,000	63,800,000	1,074	910 1.016	
Dec. 3	1,080,000	0	0	1	0	0	99	0	11,900,000	39,900,000	1,540	324 1.015	41
1926 Jan. 14	54,000	0	0	0	0	0	100	0	2,650,000	4,020,000	988	980 1.007	
Mar. 16	476,000	0	2	1	0	0	97	0	2,980,000	3,900,000	1,364	451 1.010	
April 20	198,000	0	0	0	0	0	100	0	5,360,000	2,340,000	1,571	496 1.012	

PATHOLOGICAL OBSERVATIONS

Only the kidneys and portions of spleen, lungs and liver were obtained for postmortem examination.

The kidneys were somewhat large, measuring 14 × 7 × 5 cm. The capsules stripped easily, leaving a smooth surface which was distinctly yellowish in color. The cut surfaces except for some opacity and the yellowish discoloration showed nothing abnormal. The renal arteries of both kidneys were somewhat thickened and definitely dilated.

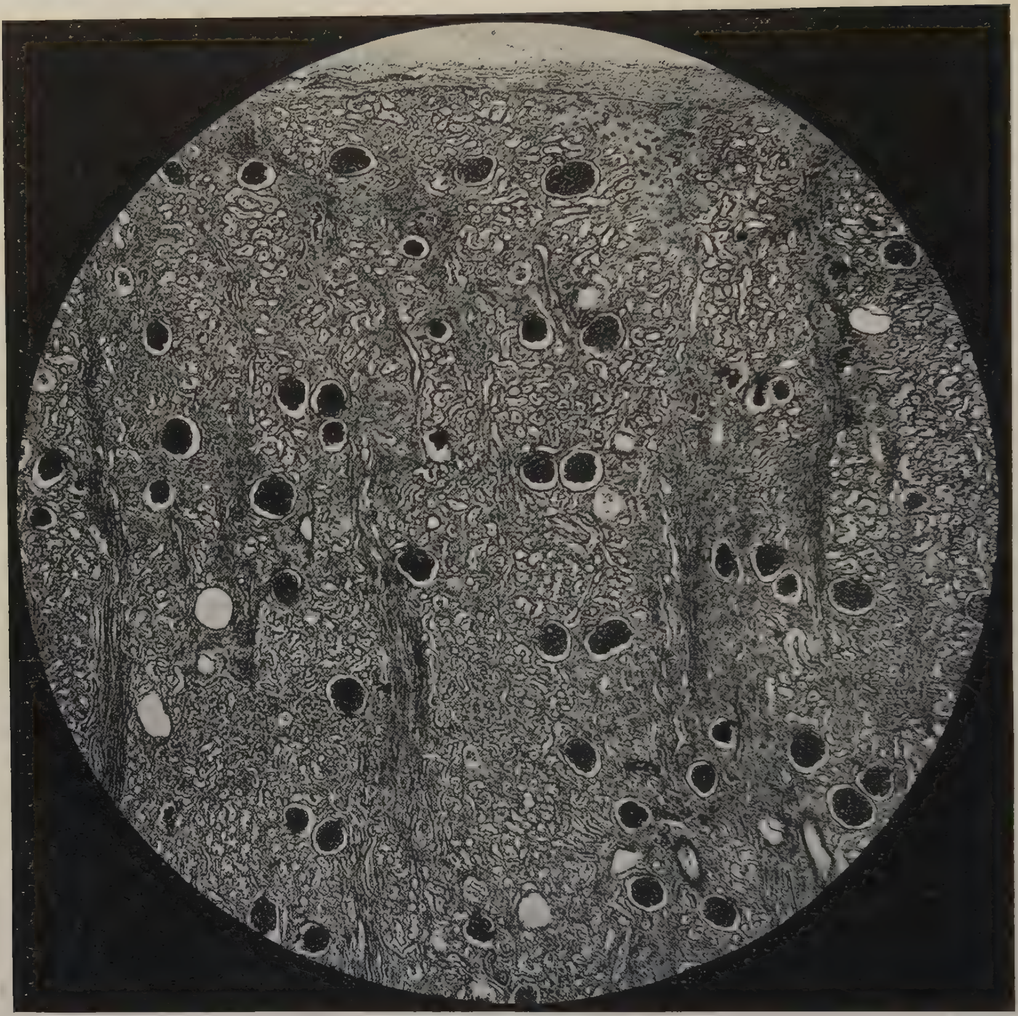

Plate LXIX a

There is a rather marked irregular scarring of the cortex which has reached the surface and forms an adhesion to the capsule. In these areas the tubules and glomeruli are atrophied. In the areas comparatively free of connective tissue proliferation the glomeruli are hypertrophied.

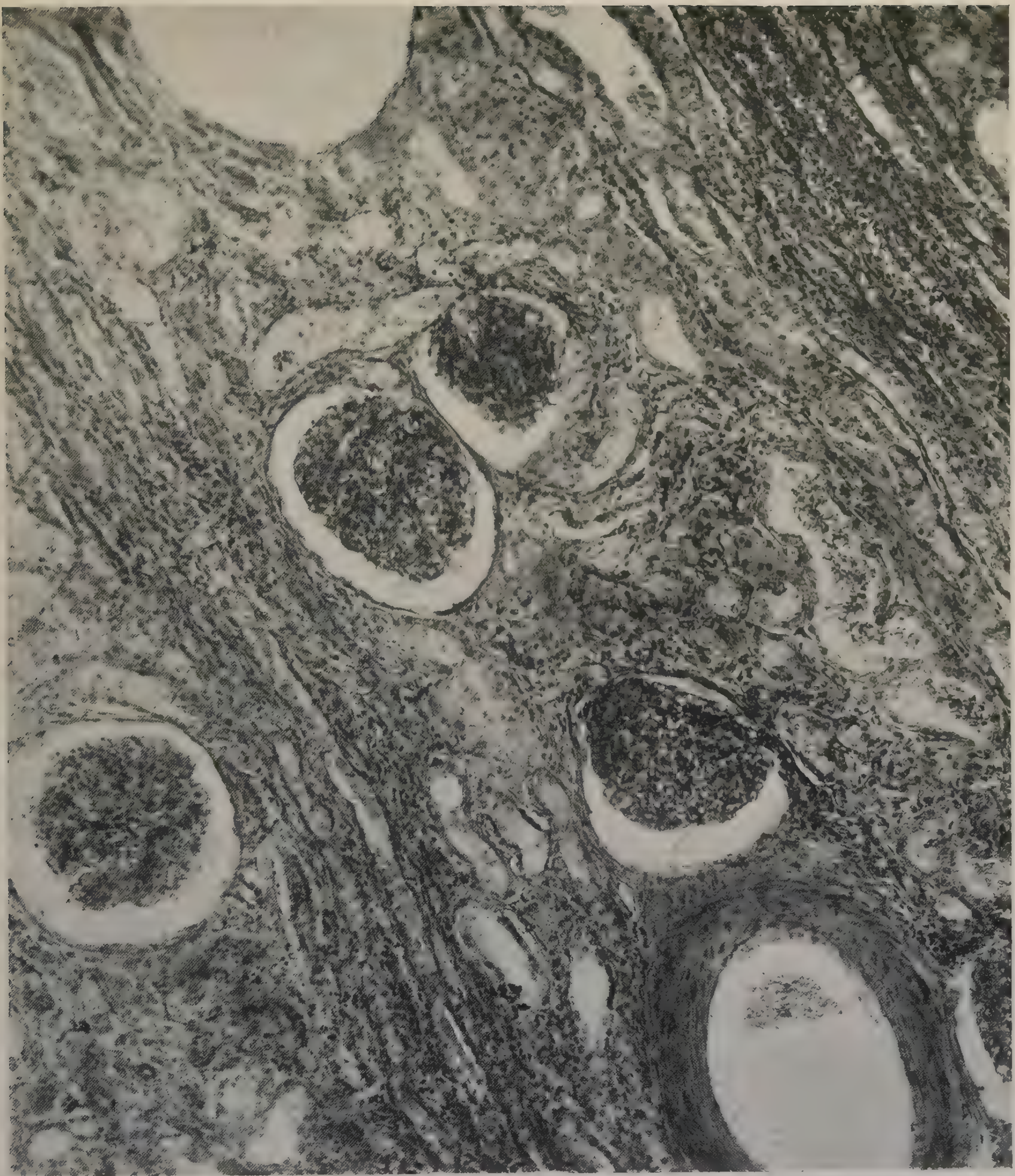

Plate LXIX b

The irregular scarring in the interstitial tissue is seen with distortion of the tubules. The glomerular tufts are still fairly well preserved. There is a moderate sclerosis of the artery.

The piece of spleen and lungs show a marked congestion, and there was a cyanotic atrophy of the liver tissue.

MICROSCOPICAL EXAMINATION

Sections of spleen show a marked dilatation of the venous sinuses and a severe hyaline degeneration of the arteries. The sections of liver show the typical picture of a chronic cyanotic atrophy with the development of considerable amount of connective tissue. The sections of lungs show the same marked congestion.

KIDNEYS. *Glomeruli.* In those parts of the cortex which are free of fibrosis the glomeruli are practically normal. Some of them are rather larger than normal and the capillaries of the tuft are distended with blood, but the intracapillary connective tissue is not increased and the capsular space is free of exudate. In the fibrous scars of the cortex the glomeruli show varying degrees of fibrosis and atrophy. In some there are still patent capillaries, while in others the tuft has been transformed into a solid hyaline mass of connective tissue.

Tubules. In the regions of scarring the convoluted tubules are compressed to a greater or lesser degree. Some are almost completely atrophied and their epithelium consists of a simple low layer of undifferentiated cells. In the free areas, the tubules are of normal size or even larger than normal. Their epithelium is definitely swollen, and the protoplasm of the cells is very granular. In scattered areas, groups of tubule cells show a severe fatty degeneration. The lumens of the convoluted tubules are in most cases empty. Occasionally a granular or hyaline cast is present. The broad ascending limbs of Henle's loop show the same degeneration. The collecting tubules are practically normal, though a greater number of hyaline casts are present than elsewhere.

Interstitial Tissue. There is a diffuse scarring of the cortex and a considerable portion of it is infiltrated with new-formed connective tissue which forms irregular scars in which the parenchyma shows the atrophy previously described. In this fibrous tissue there are a moderate number of lymphocytes.

Arteries. All of the arteries show a moderate fibrous thickening of their intima. Even the smaller branches in the cortex are involved in the arteriosclerotic process. Around the larger arteries between the cortex and medulla there is considerable fibrosis and a moderate round cell infiltration.

SUMMARY

The kidney shows a moderate arteriosclerosis of its vessels with considerable fibrosis of the cortex. Associated with this is a moderately severe parenchymatous degeneration of the epithelium of the convoluted tubules.

Case lxx

Joe R. Aged forty-three.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Etiology. Lead?

Duration. Unknown but more than three years. Observed during the last seven months.

Course. In September 1917 he suffered from what was thought to be lead poisoning. He nevertheless continued his work as a painter and after several recurrences found in March 1919 that his vision was dim. An optic atrophy was found. When seen in March 1920 there was pronounced hypertension and retinal hemorrhages and arteriosclerosis as well as optic atrophy were observed. The urine was clear and in a very large number of examinations only once contained macroscopic blood. The casts were mainly of the hyaline variety but a few renal failure casts were usually found. The amount of functioning tissue was about 20 per cent of the normal but during the seven months of observation there was no decrease in renal tissue. Death was sudden and unexplained.

RELEVANT CLINICAL DETAILS

There were no occurrences in the past history of this patient which suggested that he might have passed through the initial stage of a hemorrhagic Bright's disease. Aside from the usual diseases of childhood he had had good health, and had been steadily engaged in his work as house painter until September 1917 when he first suffered from severe paroxysmal abdominal pain associated with obstinate constipation. In spite of repeated recurrences of these symptoms and a dimness of vision which began in the Spring of 1919, he continued in the same occupation until December 1919.

He was first seen in March 1920. At this time his principal complaints were severe headache, and a gradually increasing dimness of vision. The discs were pale. The retinal arteries were narrow and tortuous and scattered over the retinal fields were numerous small hemorrhages. The heart was enlarged. The systolic pressure was 250 and the diastolic 150. There were no cardiac symptoms. The red blood cell count was over 4,000,000 per cubic millimeter. The urine was clear and in twelve hours 720 mg. of protein were excreted. The volume of urine was actually smaller when large amounts of water were drunk than when no fluids were taken. Yet the specific gravity was not always low. Readings as high as 1.020 were sometimes observed. On account of the inhibition of renal activity produced in this patient by drinking considerable amounts of water no accurate measure of the amount of functioning renal tissue was obtained, but several observations made when renal activity was not depressed showed that probably from 20 to 24 per cent of the normal amount of renal tissue was still functioning.

The patient's headaches were to a great extent relieved by a rigidly low salt diet and no further retinal hemorrhages occurred. There seemed to be no good

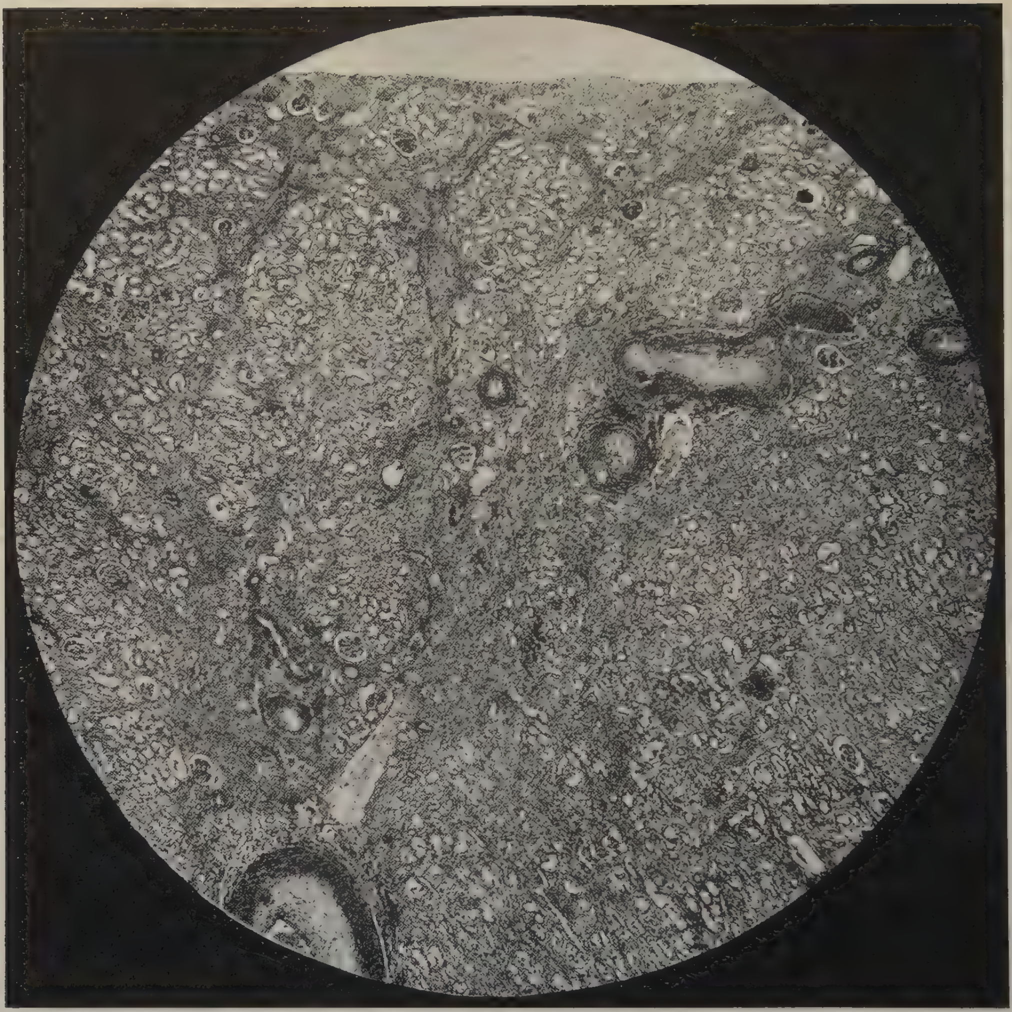

PLATE LXX A

Many arteries, including both the large and small branches to the cortex, show an extreme sclerosis. There is an extensive and irregular proliferation of the interstitial connective tissue and associated with this a heavy infiltration with leucocytes. In the scars, both tubules and glomeruli show extensive destruction. Otherwise the tubules and to a lesser degree the glomeruli are fairly well preserved.

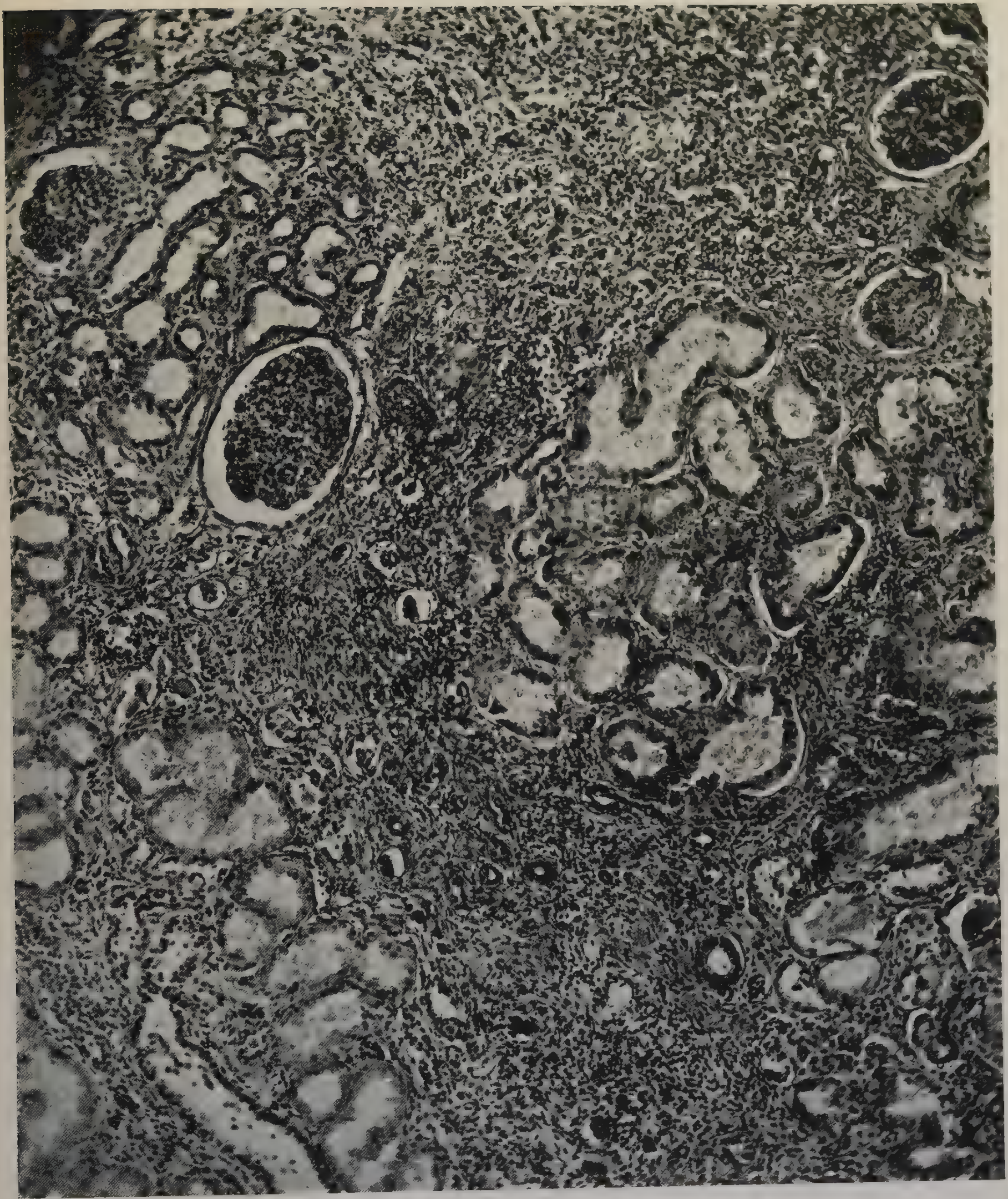

Plate LXX b

There is a marked inflammatory infiltration and proliferation throughout the interstitial tissue. The tubules are either collapsed or their epithelium shows degenerative processes. The glomerular tufts show an increase in nuclei or are fibrous.

reason why he might not live for a considerable time in comparative comfort. But on September 31, 1920, he complained of a sudden severe pain in his head accompanied by a sense of impending death. It does not appear from the account given by his relatives that there was any paralysis or unconsciousness but two hours later, after a few minutes of irregular breathing, he died. As it was only possible to obtain permission to examine the kidneys the immediate cause of death remains uncertain.

Unfortunately the methods for estimating the number of formed elements in the urine had not been developed at the time when this patient was under observation. Red blood cells were certainly not present in large numbers except on one occasion when a note was made that the centrifugalized deposit was brown. The casts were all granular or waxy and drawings made at the time show that a few of them were broad. In the absence of more definite data on the urine it is not possible to decide between the terminal stage of an unsuspected hemorrhagic Bright's disease and an unusually advanced degree of renal arteriosclerosis. The history is in favor of the supposition that the lesion was simply arteriosclerostic and that the quite exceptionally extensive destruction of renal tissue in this case was the result of the additional factor of chronic lead poisoning.

PATHOLOGICAL OBSERVATIONS

The kidneys only were obtained at autopsy. The right kidney measured 11 × 5 × 4 cm. Its capsule was somewhat adherent but stripped easily, leaving a finely granular greyish red surface in which is an occasional cyst averaging 5 mm. in diameter. The cut surface was very firm, the cortex rather narrow and the arteries prominent. The right kidney was the same as the left.

MICROSCOPICAL EXAMINATION

Glomeruli. Approximately one-half of the glomeruli are essentially normal. The remainder, which are those which lie in areas of fibrosis, show obliterative changes due to fibrosis, varying in degree from slight involvement to total hyalinization. In some of those that lie in the fibrosed areas there is a dilatation of Bowman's space which is filled with coagulated hyaline material and there is a collapse of the glomerular tuft. In none of the capsular spaces is there inflammatory exudate, nor are there hemorrhages into them. There is, however, a very definite increase in the nuclei of the tufts, and this is found to be the result of leucocytic infiltration of the tissues. The majority of these cells are mononuclear, but polymorphonuclears are present in considerable numbers.

Tubules. The epithelial tissues in the areas free of fibrosis are either of normal size and their epithelium is apparently normal, or there is a definite increase in the size of the tubules with hypertrophy of the epithelium. In the regions of fibrosis collapse of the tubules with atrophy of the epithelium is present. Other tubules in these areas are markedly dilated, lined with an atrophied epithelium and filled with coagulated colloid-like material. In the straight tubules of the medulla there is a moderate number of casts, chiefly of the hyaline type.

Interstitial Tissue. There is a marked increase in the connective tissue especially in the cortex. These large scars, consisting of fibrous connective tissue, run irregularly through the cortex, obliterating the parenchymatous elements to a greater or lesser degree as previously described and leaving free on the other hand areas where the tubules and glomeruli are either normal or hypertrophied. There is an irregular leucocytic infiltration of these scars with leucocytes of predominantly mononuclear type, but also with a certain number of polymorphonuclears.

Arteries. All of the arteries show an extreme fibrous thickening of their intima. In some of the smaller arterioles of the cortex this proliferation has almost obliterated the lumen of the vessel.

SUMMARY

The kidney shows a marked sclerosis of the arteries and a fibrosis and an inflammatory leucocytic infiltration of the interstitial tissue with obliteration and destruction of tubules and glomeruli.

CASE LXXI

Henry S. Aged fifty-two.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Duration. Unknown. Symptoms for four months before death.

Etiology. Unknown.

Course. Without any apparent reason he began four months before his death to suffer from general weakness, loss of appetite and nausea, slight breathlessness on exertion and edema of the ankles. These symptoms did not become appreciably more marked but in another month he also had cramps in his thighs and calves at night, and a throbbing in his ears. When seen two weeks before his death the urine sediment indicated an active degenerative lesion. By that time there was an intense retinitis with marked loss of vision. After a gastric hemorrhage vomiting and diarrhea set in but just before his death the blood urea concentration was only 92 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

The patient was Japanese and was able to understand or talk English with difficulty. Apparently he knew nothing about his family history. He said that apart from one minor ailment he had been quite strong and well all his life. Four and a half months before his death while he was still free from symptoms he had learned through an insurance examination that his blood pressure was too high. It was two weeks later that he began to become aware of a general weakness and tiredness accompanied by loss of appetite and occasional nausea. He noticed too that he became short of breath on moderate exertion and it seemed to him that at night there was some swelling of his ankles. About a month later still other symptoms developed. At night he had severe cramp-like pains in his thighs and calf muscles and there was constantly a dull pain in his back. It was then also that he first felt a throbbing in his ears which made it difficult for him to get to sleep. But it was not until seven weeks before his death that he became seriously alarmed about his condition when he found that his vision was blurred.

He was first seen two weeks before his death. He was not acutely ill. There was no dyspnea at rest though his lips were slightly cyanosed. There was no edema. There was a slight anemia, the red cell counts averaging about 3,000,000 per cubic millimeter, with 46 per cent hemoglobin. The pulse rate was 80 per minute and quite regular. The palpable arteries were not tortuous or calcified. There was no evidence of cardiac enlargement. The retinal arteries were arteriosclerotic. The fundi were sprinkled with recent hemorrhages and there were extensive deposits of exudate. The blood pressures taken by the staff during his stay in the hospital were interesting because they showed that in this patient there was not the usual maintenance of a constant high pressure level, but a fluctuation without obvious reason between 230 systolic and 140 diastolic as a maximum to 180 systolic and 100 as a minimum.

A concentration test gave a volume of 694 c.c. per twelve hours with a specific gravity of 1.015. There were 347,000 casts, of which as many as 79 per cent were granular. There were 2 per cent of renal failure casts, 5 per cent were waxy and 14 per cent hyaline. The number of red blood cells was 2,360,000 per twelve hours with 3,600,000 epithelial and white blood cells, most of them probably renal cells. The blood urea concentration was only 41 mg. per 100 c.c. The evidence of the urinary sediment indicated a predominantly degenerative lesion and in view of the general clinical findings it was thought that this might be the expression of a defective blood supply to the kidney due to a rapidly advancing occlusion of the renal arterioles.

During the last week of his life the patient was under the care of Dr. Garnett Cheney, to whom we are indebted for the kidneys for which only could permission for examination be obtained. He had a severe gastric hemorrhage. The blood pressure rose to 300 systolic and 150 diastolic. There was persistent vomiting, diarrhea, and at the end anuria. The blood pressure fell before death to 200 systolic and 92 diastolic. The blood urea concentration was 92 mg. per 100 c.c.

PATHOLOGICAL OBSERVATIONS

Only the kidneys were available for study after death. They were approximately of normal size, averaging 11 × 6 × 4 cm. Their capsules stripped with some difficulty, leaving a slightly granular surface of reddish purple color. The cut surface showed some fibrosis of the cortex. The renal arteries were thickened.

MICROSCOPICAL EXAMINATION

Glomeruli. All of the glomeruli are involved in an old inflammatory process. Many of the tufts are enlarged as a result of both the development of fibrous connective tissue and leucocytic infiltration. The leucocytes are chiefly of the mononuclear type but many polymorphonuclears can be found. The capillaries of the tuft are compressed by these processes and Bowman's space is obliterated to a greater or lesser degree by fibrous adhesions. The spaces still remaining patent contain granular debris and occasionally a typical capsular crescent can be found. Other glomeruli are reduced in size by the contraction of the connective tissue in their tufts and some are composed of a mass of hyaline material.

Tubules. There are still present fairly large areas of cortex where the convoluted tubules maintain their normal architecture. They show however a marked cloudy swelling of their epithelium and in many places necrosis and desquamation have occurred. The lumens of these tubules contain granular material or hyaline or granular casts and occasionally a blood cast or masses of polymorphonuclear leucocytes. In other regions where there is more proliferation of the interstitial connective tissue the tubules are compressed and lined with an atrophied epithelium. An occasional large renal failure cast can be found in the collecting tubules.

Interstitial Tissue. There is a marked irregular proliferation of the intertubular connective tissue throughout the cortex. This tissue is fibrous, but still quite

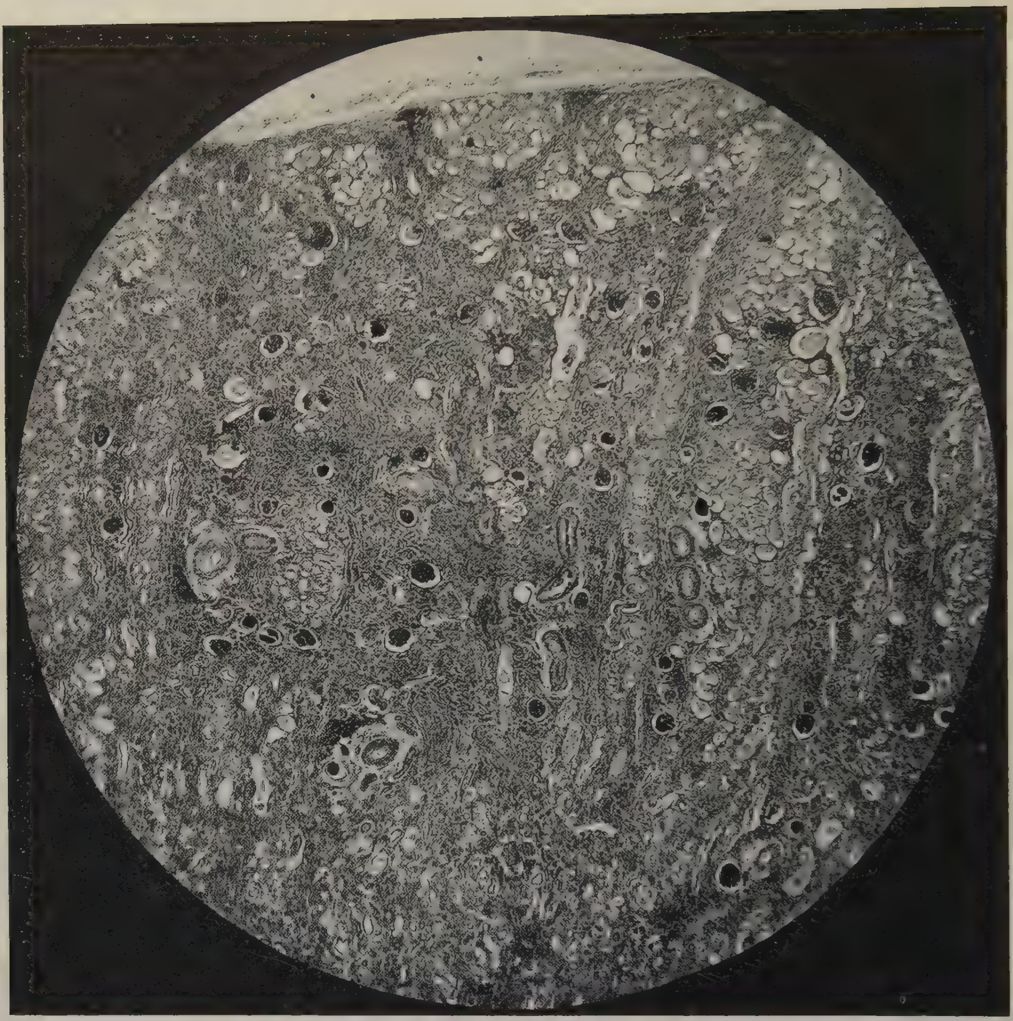

Plate LXXI a

There is a diffuse irregular inflammatory proliferation with round cell infiltration throughout the cortex and as a result there are large areas where the tubules are collapsed. The glomeruli are either enlarged or contracted from the inflammatory processes in them. Scattered through the section are seen the markedly thickened small branches of the renal artery.

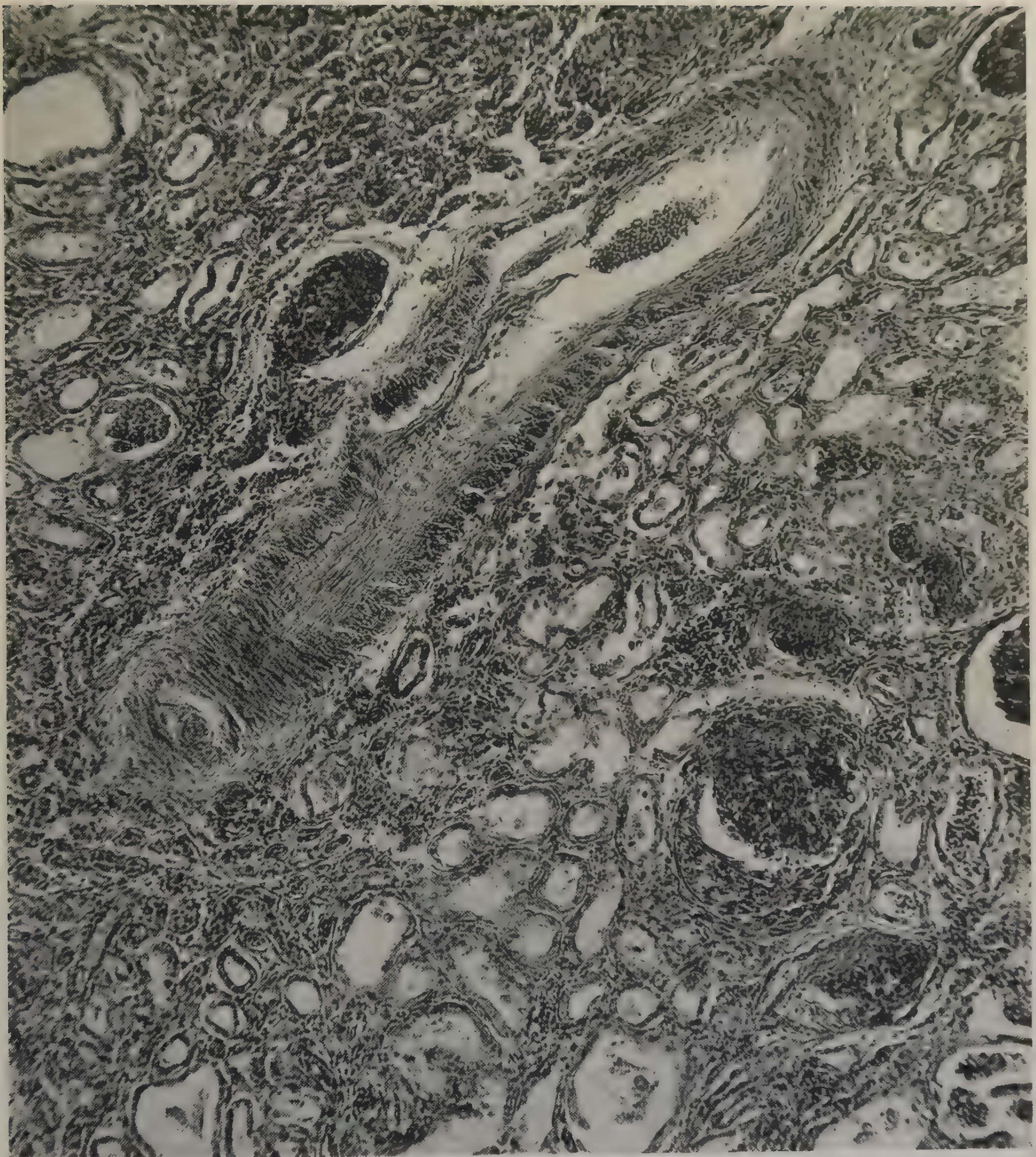

Plate LXXI b

In the glomeruli are seen definite inflammatory processes, a capsular crescent being plainly evident. The interstitial tissue is heavily infiltrated with leucocytes. There is a marked degeneration of the tubular epithelium and a moderate sized artery is greatly thickened.

cellular. Fibroblasts and great numbers of leucocytes, the latter chiefly mononuclears, though polymorphonuclears are present, are scattered throughout the fibrous material. Slightly retracted scars are formed where this tissue reaches the free surface of the cortex.

Arteries. There is a very marked fibrous thickening of the intima of the larger arcuate arteries and the adventitia of many of them is infiltrated with round cells. The smaller interlobular branches to the cortex also show a marked fibrous thickening of their walls.

SUMMARY

The glomeruli and interstitial tissue show fairly well-advanced but still active inflammatory processes. There are severe degenerative changes in the epithelial elements and a few renal failure casts are present. The arteries are greatly thickened.

CASE LXXII

Samuel S. Aged forty-four.

Clinical Diagnosis. Arteriosclerotic Bright's disease.

Etiology. Unknown.

Duration. Hypertension for seven years. Observed during the last five months.

Course. In 1914 a moderate degree of hypertension was noted. In 1919 the pressure level was higher and after 1920 the systolic pressure was always over 200. From 1919 onwards he suffered from recurrent headaches and was easily tired. In June 1921 he began to complain of dyspnea on exertion. When seen at that time the urinary sediment showed no indication of any active inflammatory or degenerative process, and the blood urea concentration was within normal limits. As the heart gradually failed a large amount of albumin appeared in the urine and towards the end a number of renal failure casts but on the day of death the blood urea concentration was only 83 mg. per 100 c.c.

RELEVANT CLINICAL DETAILS

The patient had always been strong and active and remembered no serious illnesses or infections. In 1914 he applied for life insurance and was told that his systolic blood pressure was 145 and in 1919 a casual examination gave a reading of 170. During these years his health was excellent with the exception that he had occasional pain on urination associated with the passage of gravel, and an attack of pain and swelling in one of his big toe joints which was diagnosed as gout.

Towards the end of 1919 he found that he became very tired after the day's work, and shortly afterwards he complained of headaches. He consulted a doctor who found that his systolic blood pressure was over 200. His tonsils were removed and he was kept in bed for two months on a milk and vegetable diet. The systolic pressure fell at times as low as 160 and the headaches were less severe, but thereafter he was even weaker and more easily tired than before.

He was seen for the first time in June 1921. He stated that he had recently observed that he was very short of breath when he climbed the stairs in his house. Examination revealed no thickening or tortuosity of the large arteries. One oculist found normal retinal vessels, another considered that slight arteriosclerotic changes could be detected. The systolic pressure was 220 and the diastolic 150. There was no increase in pulse pressure after exercise. The heart was enlarged but the contractions were forcible and regular. The *x*-ray shadows of the aorta revealed no abnormality. Towards the evening of any day during which he was out of bed, a definite pitting edema appeared in the feet and ankles and moist râles could at times be heard at the bases of both lungs. There was no anemia. Measurements of day and night collections of urine showed a pronounced nycturia. The volumes of concentration tests were large but the specific gravity was always over 1.020. The number of casts in the urinary sediment was not large and there was no marked

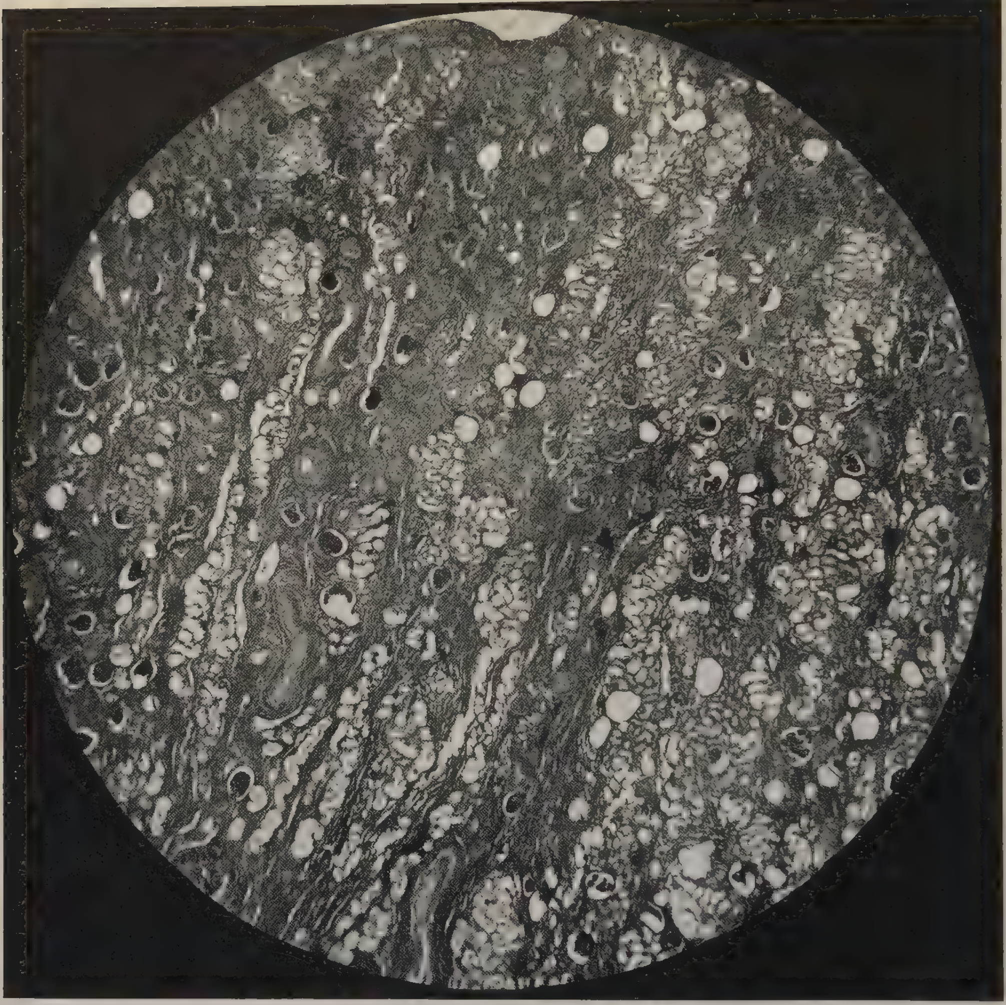

Plate LXXII a

The thickened arteries throughout the section are plainly seen as well as the dense almost hyaline scar tissue which diffusely infiltrates the cortex. The usual destruction of glomeruli and tubules in such areas is plain. There is a marked hypertrophy of the epithelium in the relatively free portions of the cortex. In these tubules marked degenerative lesions are observed.

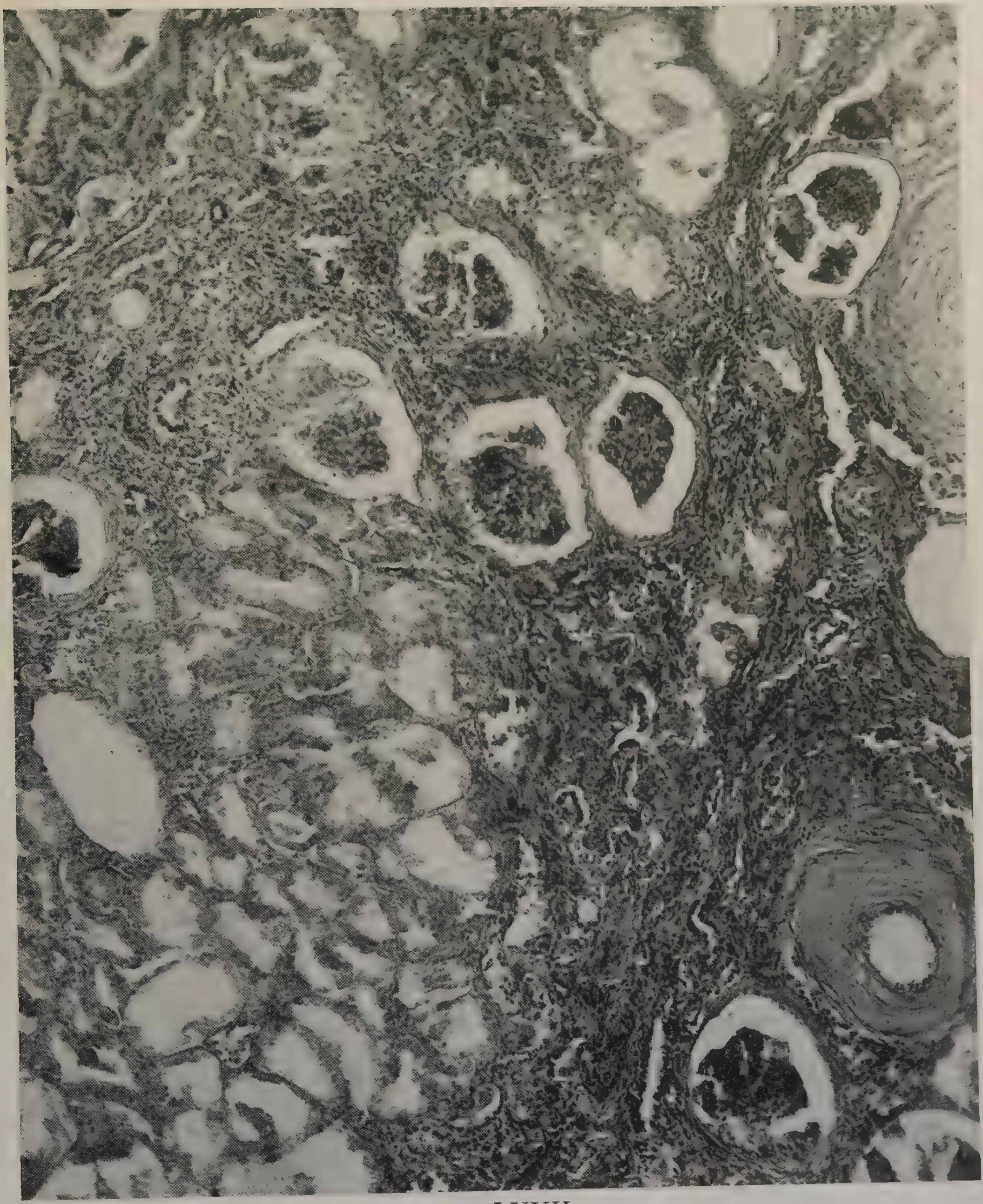

Plate LXXII b

The sclerotic arteries are seen in the right part of the figure. The glomerular tufts surrounded by scar tissue are markedly distorted and compressed. There are marked degenerative changes in the epithelium in the tubules which lie free of the area of scarring, in the lower left portion of the figure.

excess of red blood cells or of white blood cells or epithelial cells but the presence of a certain percentage of epithelial, granular and waxy casts suggested the occurrence of some degree of desquamation of the tubule cells. There were no renal failure casts. The blood urea concentration was 31 mg. per 100 c.c. An attempt to determine the amount of functioning renal tissue failed because it was impossible to produce diuresis.

His subsequent history was that of a slowly but steadily progressive cardiac failure. The diastolic pressure never fell below 135. The edema of the legs and lungs became gradually permanent and more and more pronounced. The rate of protein excretion increased and in September averaged about 5000 mg. per twelve hour period. In October a considerable percentage of the casts were of the renal failure type. A series of blood urea determinations from the time he was first seen up to the day of his death gave no evidence of any progression in the extent of the renal lesion. He died in November 1921 from cardiac failure.

PATHOLOGICAL OBSERVATIONS

At autopsy there was found a general arteriosclerosis with cardiac hypertrophy, a healed apical pulmonary tuberculosis, ascites and hydrothorax. The kidneys were reduced in size, measuring 9 × 4 × 2 cm. The capsule was rather adherent and stripped with some difficulty, leaving a purplish red irregularly scarred surface. The cut surface showed a reduction and fibrosis of the cortex and a definite thickening of the renal arteries.

MICROSCOPICAL EXAMINATION

Glomeruli. About half of the glomeruli are still fairly well preserved, their tufts showing no fibrosis and their capillaries being patent. The remainder, enclosed in or lying near a mass of scar tissue, show varying stages of fibrosis and hyalinization. No exudative inflammatory changes are present in any of them, such as the presence of polymorphonuclear leucocytes or exudate or red blood cells in Bowman's space.

Tubules. In the free areas of the cortex the convoluted tubules are essentially normal in shape, though some are increased in size. In practically all there is an extensive granular degeneration of the epithelium with necrosis and desquamation and the lumens of the tubules contain granular material. In the areas of scarring the tubules are compressed and collapsed and their epithelium is atrophic. In the collecting tubules occasional large renal failure casts are seen. No red blood cells or polymorphonuclears are present in any of the tubules.

Interstitial Tissue. The cortex is replaced in more than one-half its extent by the development of dense fibrous connective tissue. This tissue is composed principally of collagen fibrils, though scattered connective tissue cells and mononuclear leucocytes may be found. Deep retracted scars are formed where it reaches the free surface.

Arteries. All of the arteries from the arcuate through the interlobular to the afferent glomerular arterioles show a severe arteriosclerosis. The intima and the entire wall of the smaller arteries show a marked fibrous thickening.

SUMMARY

The arteries show a severe sclerosis and there is extensive proliferation of the interstitial connective tissue. The glomeruli and tubules are atrophied in the areas of scarring. The tubules show rather marked parenchymatous degeneration. No exudative inflammatory processes are present.

CHAPTER VIII

A CLINICAL SUMMARY AND COMPARISON OF CLINICAL AND PATHOLOGICAL DATA

Chapter VIII

A CLINICAL SUMMARY AND COMPARISON OF CLINICAL AND PATHOLOGICAL DATA*

In the presentation of the clinical facts about these patients the thought and effort of investigators in every land whose work relates to our problem has apparently been ignored and certainly has been almost entirely unmentioned and unacknowledged. But to those who have been or are now engaged in such studies, either directly, in the clinical field, or indirectly, but certainly no less effectively through their work on the anatomy and physiology of the kidney, it will be unnecessary to point out that the neglect is only apparent. This monograph is addressed to them alone and they will see and understand how entirely our views rest on the results of their labors. And just as on the historical side much can safely be left to implication, so in summarizing the clinical results we need not discuss the differences between this particular classification and those which have been evolved in the past or are now in use. For this classification does not run counter to the clinical observations of the past, but on the contrary is almost wholly based on them. The new methods are only the old methods so modified that we obtain quantitative instead of merely qualitative results, and so used that wherever possible the whole history of the renal lesion is outlined from the beginning to the end. It is unnecessary to review again the reasons why the endeavor was made to derive from the ancient and largely discarded discipline of urinary microscopy a clinical answer to the question as to the nature of the renal lesion or again to detail the experimental observations which led to the finding of the conditions under which the extent of the lesion may be estimated from functional results. All that remains now is to compare the results of these methods with the anatomical facts. For the final judge in this matter is the Pathologist.

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* T. A.

But to the pathologist, no matter how sympathetic with clinical endeavors, it is immaterial whether a clinical device may or may not, in some degree, or at some point or other, be used for the prediction of the structural effects of renal lesions. For nothing is more certain than that the methods we have used can give at best only a partial and distorted picture of the results of a pathological process. This is necessarily so, since, in relation to the question of the nature of the renal lesion, we are limited to an examination of those cellular elements and structures which are detached from the kidney and are carried to the exterior in the urine. It follows that whenever in any renal unit a lesion leads to the cessation of urine formation we are deprived of all direct evidence not only of the nature of the lesion in that part of the kidney but even of its very existence. And, of course, we can never through such methods obtain material on which to form a judgment as to vascular and interstitial lesions, factors of the utmost importance for the development of those lesions which are clinically significant. Obviously to ask whether active lesions in still functioning glomeruli and tubules provide sufficient evidence to enable the clinician to make anatomical predictions as to the nature of the predominant renal lesion is a question which is of interest only as a means for the evaluation of these particular methods and the answer can have no particular interest for the pathologist who has for his material the entire range of structural effects. It is proper therefore that the clinical author should subject his data to the test of a comparison with those anatomical results to which he is restricted by means of the limitations of his methods. The development by the Pathologist of the whole subject of the pathology of kidney in Bright's disease will reveal how narrow is the realm within which clinical methods can as yet hope for any success. But the invention of methods of wider usefulness in this field rests largely on an appreciation by clinicians of such results and of such questions as are dealt with by the author of the pathological sections who understands clinical difficulties but has developed his theme without respect to the present immaturity of clinical medicine.

The clinical work was begun and continued in the hope that the nature and extent of the renal lesion might be ascertained by means of quantitative studies of the urinary sediment and of the amount of functioning renal tissue, in combination, of course, with the use of already existing clinical methods. It was hoped that through these methods the physician might be enabled to follow the development of the pathological process throughout the lifetime of the patient. The extent to which these hopes have been realized is to be measured by the degree to which the clinical predictions at the time of the death of the patient correspond with the actual anatomical findings of the Pathologist. In Table XXXIX the last observations before death are given for comparison with the Pathologist's summary.

A survey of these summaries reveals two negative but important factors. We can, first of all, at once eliminate the idea that in the hemorrhagic group the lesions are entirely inflammatory, in the degenerative only degenerative or in the arteriosclerotic group solely arterial and atrophic. Secondly it is evident that in the hemorrhagic group the lesions are not restricted to the glomeruli, that in the degenerative cases there may be lesions elsewhere than in the tubule cells* and that in the arteriosclerotic group the pathological process extends beyond the confines of the vascular and interstitial tissues.

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* In purely degenerative lesions the glomeruli show no active glomerulitis but they do not escape damage. Signs of degeneration of the glomerular endothelium and epithelium, in the form of fat droplets, have often been demonstrated, and this lesion precludes the use of such a clinical term as "tubular nephritis." It seems likely that it is a glomerular lesion which leads to the high rate of protein excretion found in all cases in which there is evidence of an intense degenerative process in the kidney.

The positive correlations become apparent when the anatomical observations are subjected to statistical analysis. The Pathologist speaks of "glomerulitis," of "degeneration of the parenchymal tissue," of "interstitial proliferation" and of "arteriosclerosis" or "endarteritis." If these terms are set down opposite each of the three clinical groups and the presence or absence of the processes they designate is indicated by a + or a − sign, or by the sign ± when the lesion may or may not be present, the arrangement shown in Table XL is the result.

TABLE XL

GENERAL SUMMARY

THE ANATOMICAL SIGNIFICANCE OF THE THREE CLINICAL DIVISIONS

Clinical	Pathological			
	Glomerulitis	Parenchymal degeneration	Interstitial proliferation	Arteriosclerosis or endarteritis
Hemorrhagic	+	±	±	±
Degenerative	−	+	±	±
Arteriosclerotic	−	±	+	+

This table is a summary statement of the anatomical meaning of the clinical classification. In Table XLI the data on which these generalities are based are given for each individual case.

The first and most important conclusion of the general table is that glomerulitis as defined by the Pathologist is found only in hemorrhagic Bright's disease. In Table XLI there are 2 cases which do not conform to this rule. In one of them (Case LVII), classed clinically as degenerative, three counts showed no increase in red blood cell excretion and yet an active glomerulitis was found in the sections. In this case there was a very intense degenerative lesion (the child was dying from a staphylococcal pyemia) and the urine was always opaque with epithelial cells and precipitated globulin.

Table XLI

Incidence of Different Anatomical Lesions in the Three Varieties of Bright's Disease

I. HEMORRHAGIC BRIGHT'S DISEASE

	No.	*Glomerulitis*		*Parenchymal Degeneration*	*Interstitial Proliferation*	*Arteriosclerosis or Endarteritis*
		Active	*Chronic*			
Active stage.......	I	+	−	+	+	−
	II	+	−	+	+	−
	III	+	−	+	+	−
	IV	+	−	+	+	−
	V	+	−	+	+	−
	VI	+	−	+	+	−
	VII	+	−	+	+	−
	VIII	+	−	+	+	−
	IX	+	−	+	+	−
	X	+	−	+	+	−
	XI	+	−	+	+	+ (age?)
	XII	+	−	+	−	−
	XIII	+	−	+	+	−
	XIV	+	−	+	+	−
	XV	+	+	+	+	−
Latent stage.......	XVI	+	−	+	−	−
	XVII	(abscess)	−	+	+	−
	XVIII	+?	−	+	+	+ (age?)
	XIX	+	−	+	−	−
	XX	+?	−	−	+	+ (age?)
Terminal stage.....	XXI	+	+	+	+	+
	XXII	+	+	+	+	+
	XXIII	+	+	+	+	−
	XXIV	+	+	+	+	+
	XXV		+	+	+	+
	XXVI	+	+	+	+	+
	XXVII	+	+	+	+	+
	XXVIII	+	+	+	+	+
	XXIX	+	+	+	+	+
	XXX		+	+	+	+
	XXXI	+	+	+	+	+
	XXXII		+	+	+	+
	XXXIII	+	+	+	+	+
	XXXIV		+	+	+	−

TABLE XLI.—(*Continued*)

	No.	*Glomerulitis*		*Panrechymal Degeneration*	*Interstitial Proliferation*	*Arteriosclerosis or Endarteritis*
		Active	*Chronic*			
Terminal stage....	XXXV		+	+	+	+
	XXXVI		+	+	+	+
	XXXVII		+	+	+	+
	XXXVIII		+	+	+	+
	XXXIX	+	+	+	+	+
	XL	+	+	+	+	+
	XLI	+	+	+	+	+
	XLII	+	+	+	+	+
	XLIII	+	+	+	+	+
	XLIV	+	+	+	+	+
	XLV	—	—	+	+	+
	XLVI	+	+	+	+	+
II. DEGENERATIVE BRIGHT'S DISEASE						
Cryptic form......	XLVII	—	—	+	—	—
	XLVIII	—	—	+	—	—
	XLIX	—	—	+	—	—
	L	—	—	+	+	+ (age?)
	LI	—	—	+	—	—
Pyogenic form.....	LII	—	—	+	—	—
	LIII	—	—	+	+	+ (age?)
	LIV	—	—	+	+	—
	LV	—	—	+	+	
	LVI	—	—	+	—	—
Bacterial form.....	LVII	+	+	+	+	—
Non-bacterial form.	LVIII	—	—	+	—	—
	LIX	—	—	+	—	+ (age?)
III. ARTERIOSCLEROTIC BRIGHT'S DISEASE						
	LX	—	—	+	+	+
	LXI	—	—	—	+	+
	LXII	—	—	+	+	+
	LXIII	—	—	—	+	+
	LXIV	—	—	+	+	+
	LXV	—	—	—	+	+
	LXVI	—	—	+	+	+
	LXVII	—	—	—	+	+
	LXVIII	—	—	+	+	+
	LXIX	—	—	+	+	+
	LXX	—	—	—	+	+
	LXXI	—	+	+	+	+
	LXXII	—	—	+	+	+

In the other case (Case LXXI) the symptomatology was so predominantly arterial that a clinical diagnosis of arteriosclerotic Bright's disease was made even though a rate of excretion of 2,360,000 red blood cells per twelve hours was observed at a time when there was no renal congestion due to cardiac failure. Dr. E. M. MacKay saw him a month before and finding over 10,000,000 red blood cells in his urine, correctly placed him in the hemorrhagic group. If these two cases are acknowledged as clinical errors it may be said that in this series glomerulitis occurs only in hemorrhagic Bright's disease. Is it found in every instance? Here again there are two exceptions. The first (Case XLV) is not one of any weight for it is a patient who died in 1920 before the method for counting red blood cells had been developed. Such clinically incomplete cases were included because with them began the attempt to make anatomical predictions from clinical phenomena. The second (Case XVII) had a urinary picture seven days before death which was in every respect typical of the latent stage of hemorrhagic Bright's disease but the sections showed minute cortical abscesses instead of glomerulitis. Here again the positive instances so far outweigh the negative that in a matter of this sort it seems legitimate to extend the former conclusion and to say that in this series glomerulitis is always present in hemorrhagic Bright's disease and never found in degenerative or arteriosclerotic Bright's disease. This relatively justified relation between glomerulitis and hemorrhagic Bright's disease is of clinical importance. It gives the essential anatomical warrant for the conception, derived originally from long-continued observation of individual patients as they passed through the various stages of the malady, that despite the extreme differences in their symptomatology the patients classed under this division are suffering from one and the same disease. By means of an objective clinical sign, a verifiable peculiarity of the urinary sediment, it enables the physician to unite under one category patients seen in all stages of the disease and affords him a foundation on which to commence an independent clinical study of the problems of prognosis and of etiology.

Glomerulitis is described by the Pathologist as "active" or as "old" or "chronic," and in accordance with his descriptions the presence of one or of both of these forms has been noted in Table XLI. The table shows that in the active stage only active glomerulitis is found except in Case XV, in whose kidneys the chronic as well as the active form was well developed. In this case the patient was first seen in the latent stage and was followed over years through a stage of well-marked activity until evidences of the approach of the terminal stage were noted. In the terminal cases both active and chronic glomerulitis is usually observed but there are 8 cases described as having chronic glomerulitis only or at least predominantly. Now it is evident that our clinical methods provide us with no positive criteria on which to base a diagnosis of chronic glomerulitis. Cellular proliferation and fibrosis within the glomeruli may decrease the amount of functioning renal tissue but this is a non-specific effect which may be due to many different types of renal lesion. It is of interest therefore that these 8 cases (XXV, XXX, XXXII, XXXIV, XXXV, XXXVI, XXXVII, XXXVIII) include some of the clinically most typical instances of hemorrhagic Bright's disease and that in three of them the whole development of the lesion from the initial to the terminal stage had been traced by history and observation. Except in Case XXXVIII, in which the sediment picture was obscured by a gross pyuria due to a suppurative pyelitis, even the last counts shown in Table XXXVIII are distinctive of the hemorrhagic group. It would seem therefore that even in kidneys in which the glomerulitis had become predominantly chronic there was sufficient "activity" in the still functioning glomeruli to acquaint the clinician with the probable nature of the renal lesion. In fact the persistence over years and even decades of evidence of an active inflammatory lesion in the glomeruli is the peculiar clinical characteristic of this unique disease. Yet an end of this long persistence is seen in the many fibrosed and functionless glomeruli in the kidneys of patients in the terminal stage. The other mode of termination of active glomerulitis is approached in the latent stage. In Case XVIII the pathologist speaks of a "latent or perhaps completely healed intracapillary glomerulitis" and in Case XX of "traces of a former glomerulitis." This is the end, the end of complete healing, to which nearly half of all the patients come whose course has been followed from the beginning to the end.

It is unnecessary to say anything more about degenerative or arteriosclerotic Bright's disease. The principal clinical interest lies in the possibility of separating them from the hemorrhagic group. Table XXXIX gives evidence that this is usually possible. Table XLI shows that in the degenerative group the only constant lesion is degenerative, while in the arteriosclerotic group arteriosclerosis or endartitis and interstitial proliferation are the only invariable lesions.

Chapter IX

A CORRELATION OF THE CLINICAL AND PATHOLOGICAL OBSERVATIONS

CHAPTER IX

A CORRELATION OF THE CLINICAL AND PATHOLOGICAL OBSERVATIONS*

The summary of the pathological characteristics of the various forms of Bright's disease as established by the Clinician may now be briefly made, our problem being to see in how far the groupings that he established by his clinical determinations are composed of homogeneous groups in a pathological sense. In other words if there is any unity in the processes observed morphologically in the tissues corresponding with his subdivision of the clinical cases we may reasonably assume to have established certain types of the disease.

In all the specimens from examples of hemorrhagic Bright's disease, no matter in what stage the process had been interrupted by death, hemorrhage was found in the kidney tissues. This term, suggested by the results of clinical methods, is well suited therefore to describe a prominent pathological feature of the condition. Associated with this characteristic of the disease were found other lesions, whose nature and degree varied with the state of the disease in the kidney. Inflammation is perhaps the most striking of these and occurred in all those tissues which from their nature respond to toxic irritation by this phenomenon. All stages of the process from the most acute with leucocytic infiltration, deposit of fibrin and hemorrhage to old chronic proliferative lesions where the active progress of the process was barely detectable, were found.

Since, as we have just said, the inflammation is the cause of the hemorrhage, the very pertinent question immediately arises why an effect is taken as the foundation of our classification rather than the cause. This is a matter which may be more properly discussed in a later chapter, but in passing we might state that there are many reasons, and we are concerned here only with those which interest the pathologist, which we believe make the use of the inflammatory process for this purpose unwise. For associated with it and of equal importance in the production of the total effect on the kidney are those regressive processes, the various necrobiotic degenerations and necrosis, which are the response of the epithelial elements, and the sclerotic changes, whatever their nature may be, which are found in the arteries. Then too the sum total of all these occurrences which may produce the condition in the late stages of the disease that is summarized under the term metallaxis certainly cannot be considered the effect of inflammation alone for the other processes play a definitely and equally important part in its production. However, we only wish here to state briefly the morphological characteristics as we found them in the various stages and types of Bright's disease. This may be done perhaps most easily in synoptic form and we shall leave the consideration of theoretical matters for a later time. In the following summaries therefore the average type picture of the kidney as found in the various forms of the disease is briefly summarized and the degree of correlation which obtained with the clinical observations noted.

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* J. O.

Hemorrhagic Bright's Disease

In the detailed comparison of the pathological with the clinical findings in the active and terminal stages of hemorrhagic Bright's disease certain discrepances are noted. It will be remembered that the Clinician has stated that the word "active" is "used more with reference to the general clinical picture than as a description of the renal lesion." However, since his admitted aim is a "return to the straight and narrow road of morphology" he will permit a criticism by the Pathologist of his sorting of these cases, which admitting as they do of a transition of one type of the disease to a later stage, will of necessity be difficult to place accurately by any other means than by the appearance of the actual lesions as seen in the organs themselves.

As a result of our morphological study of these two groups of kidneys we would therefore suggest the shifting of certain of these transitional cases from one group to the other. This we do not with any desire to correct minutely the minor errors to which the difficult endeavor of the Clinician is always open, but because, as will be seen later, a slight rearrangement of the individuals of the two groups on the basis of the anatomical findings permits of generalizations which aid in a clearer conception of the disease.

In Table XLII the groups as determined by the Clinician are given. Variation in the morphological findings from the general characteristics of the group are indicated by arrows. A rough estimate of the degree with which the lesions found varied from what might be considered the normal group characteristic is indicated by the length of the arrow.

Initial Stage. No cases came to post mortem examination.

Active Stage. The activity in a pathological sense was striking in this stage. Inflammatory processes of the acute type were present, such as intracapillary or extracapillary glomerulitis, hemorrhage into Bowman's space and thus into the tubules, edema and leucocytic infiltration, including polymorphonuclear, of the interstitial tissue. Regressive changes in the epithelial elements were equally active. These included cloudy swelling, fatty degeneration and necrosis and desquamation. Regenerative repair in the epithelium was usually found associated with these destructive processes. Only minor vascular lesions such as sclerosis were present.

In many of the cases, forming transitions towards the terminal stage of the disease, were found associated with the lesions just described the added process of inflammatory proliferative change in the glomeruli and interstitial tissue and in some, sclerosis of the arteries. This inflammatory fibrosis in the kidneys of those whose death was due to Bright's disease,

TABLE XLII

CORRELATION OF CLINICAL AND PATHOLOGICAL FINDINGS IN A SERIES OF CASES OF HEMORRHAGIC BRIGHT'S DISEASE

The names appear in the groups as determined by clinical methods. Variation in the morphological findings from the general characteristics of the group are indicated by arrows, a rough estimate of the degree of variation being given by the length of the arrow.

Active	Morphological evidence of transition	Terminal
	to ← →	
i. Kelly B.		xxi. Percy B.
		xxii. Frederick B.
ii. Robert B.	←	xxiii. Richard B.
		xxiv. Leila B.
iii. Marion B.		xxv. John A. B.
iv. Peter B.	←	xxvi. John B.
v. Helen F.		xxvii. Nicholas C.
vi Helen G.	→	xxviii. Nathaniel C.
vii. Henry G.		xxix. John C.
viii. Alparata H.	→	xxx. Lucy C.
ix. Eugene McV.		xxxi. Richard C.
x. George O.		xxxii. William C.
xi. Edward R.	→	xxxiii. Stewart D.
xii. James R.	→	xxxiv. Edith D.
xiii. Adolph S.		xxxv. Ernest G.
xiv. Jane S.		xxxvi. Verna G.
xv. Robert T.	→	xxxvii. Margaret G.
		xxxviii. Elizabeth G.
	←	xxxix. Charles H.
		xl. Geneva K.
	←	xli. Bertha K.
		xlii. Leo N.
		xliii. Ralph S.
		xliv. William V.

that is to kidney failure and uremia, was of the diffusely infiltrating type, the renal elements, both glomeruli and tubules having suffered quite evenly throughout the entire cortex of the kidney. Plate XI A shows such an example.

Along with such cases, however, are those whose kidneys were still sufficient though the seat of a progressive disease which might have ultimately destroyed them. These individuals died of incidental infection or circulatory failure. Some of these were of the diffuse type just described, insufficiently developed to have as yet caused impairment of kidney function. Others however were of the earlier stages of the patchy fibrosis which is so characteristic of terminal Bright's disease (Plate VI A). Evidently the

TABLE XLIII
HEMORRHAGIC BRIGHT'S DISEASE
Active Stage

	Duration in mo.	Death from	Complicated by	Type of metallactic change
I. Kelly B.	6?	uremia		diffuse
II. Robert B.	18	uremia		diffuse
III. Marion B.	1	uremia	erysipelas	diffuse
IV. Peter B.	?	pulmonary edema	uremia	diffuse
XXVI. John B*	96	uremia		diffuse
V. Helen F.	3½	uremia		diffuse
VI. Helen G.	96	erysipelas		patchy
VII. Henry G.	32	pneumonia		diffuse
XXXIX. Charles H.*	?	uremia?		diffuse
VIII. Alparata H.	?	bacterial endocarditis		diffuse
XLI. Bertha K.*	23	uremia		diffuse
IX. Eugene McV.	?	uremia		diffuse
X. George O.	10+	pneumonia		diffuse
XI. Edward R.	24?	uremia		diffuse
XII. James R.	5	circulatory failure		patchy
XIII. Adolph S.	1	bacterial endocarditis		diffuse
LXXI. Henry S.†	?	circulatory failure		patchy
XIV. Jane S.	6?	cerebral edema		diffuse
XV. Robert T.	132	uremia	dehydration	patchy

* Considered terminal stage by Clinician.

† Considered arteriosclerotic Bright's disease by Clinician.

Summary

19 cases	10 uremia	9 diffuse, 1 patchy
	4 circulatory failure	2 diffuse, 2 patchy
	5 infections	4 diffuse, 1 patchy

accident which had caused death had interrupted a disease which otherwise might have progressed to a terminal stage, but such speculation belongs in the following chapter where the course of the disease is theoretically described.

Casts of all sorts were found in the kidney tubules, especially the characteristic and never-failing blood cast, and broad renal failure casts were found in those kidneys which on account of the severity of the inflammatory fibrosis had failed, with a resulting uremia.

Latent Stage. Any or all of the processes described in the active stage were present, but as the term indicates at a low degree of activity. Considerable search might be necessary to demonstrate a glomerulus in a stage of active inflammation or to find the significant blood cast. Epithelial degenerative changes were also slight so that in some instances it was the remains of formerly active processes such as almost healed scars in glomeruli and interstitial tissue or atypical regenerated epithelium that gave the clue to nature of the lesion.*

Terminal Stage. In the strict pathological sense the terminal stage too is an active one. But the processes of inflammation and degeneration though still progressive were much less active than formerly. The condition in the kidney is approaching asymptotically as it were a limit, which anatomically is represented by complete fibrosis of the organ and functionally is expressed by uremia, for the rate of progress of the disease becomes slower as this limit is approached. Inflammatory lesions in the glomeruli and interstitial tissue were of the chronic type. Degeneration of the epithelium was present in greater or lesser degree and sclerosis of the arteries was now constantly present. The histological picture was one of patchy inflammatory fibrosis, which forms a striking contrast to the even diffuse process observed in fatal uremic cases of the active stage. (PLATE XXX A.) The important result of

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* Among the latent cases of hemorrhagic Bright's disease the Clinician has included one case which is definitely the result of embolic phenomena. It occurred in an individual suffering from bacterial endocarditis, the lesions consisting of multiple embolic abscesses. (Case XVII.) "Focal embolic nephritis," a type of kidney lesion which is a minor complication of bacterial endocarditis, was not found in our series and is omitted from the classification of Bright's disease as the term is used in the present work. True hemorrhagic Bright's disease (diffuse glomerulonephritis) is a frequent complication of bacterial endocarditis and we in fact observed two such cases which were by chance examples of the latent stage of the disease. In two other instances (Cases VIII and XIII) a bacterial endocarditis was found at autopsy and in these cases though the focal embolic lesions peculiar to this infection could be found in occasional glomeruli, the general kidney lesions were of the usual type found in active hemorrhagic Bright's disease (cf. pp. 592 et seq.).

TABLE XLIV
HEMORRHAGIC BRIGHT'S DISEASE
Terminal Stage

	Duration in yrs.	Death from	Type of metallaxtic change
XXI. Percy B.	?	uremia	patchy
XXII. Frederick B.	20+	uremia	patchy
XXIII. Richard B.	2½	uremia	diffuse
XXIV. Leila B.	2	uremia	patchy
XXV. John A. B.	3	uremia	patchy
XXVII. Nicholas C.	2½	uremia	patchy
XXVIII. Nathaniel C.	22	uremia	patchy
XXIX. John C.	19	uremia	patchy
XXX. Lucy C.	6¾	uremia	patchy
XXXI. Richard C.	?	uremia	patchy
XXXII. William C.	27	uremia	patchy
XXXIII. Stewart D.	12	uremia	patchy
XXXIV. Edith D.	6	uremia	patchy
XXXV. Ernest G.	?	uremia	patchy
XXXVI. Verna G.	7?	uremia	patchy
XXXVII. Margaret G.	5½	uremia	patchy
XXXVIII. Elizabeth G.	?	uremia	patchy
XL. Geneva K.	?	uremia	patchy
XLII. Leo N.	?	uremia	patchy
XLIII. Ralph S.	7	uremia	patchy
XLIV. William V.	?	uremia	patchy
XLVI. William Z.	50	uremia	patchy

Summary

22 cases, all uremia.. 21 patchy, 1 diffuse.

these changes was the production of the patchy metallaxis which is characteristic of terminal Bright's disease. The architecture of the entire kidney was thus altered, an effect noted in glomeruli, tubules, interstitial tissue and arteries. And as a result of these changes local circulatory alterations had developed such as irregular venous and capillary congestion. Casts of all sorts were present, depending on the nature of the lesions present, but the characteristic form was the broad renal failure cast which is typical of the failing kidney.

Degenerative Bright's Disease

Cryptic Form. In all cases the striking and significant lesions were degenerations of the epithelium of the convoluted tubule and the broad ascending limb of Henle's loop, such as cloudy swelling, fatty degeneration, both with the accumulation of isotropic and anisotropic fats, and necrosis. Inflammatory lesions in the glomeruli and interstitial tissue were lacking or of minor occurrence, nor were there significant sclerotic lesions in arteries.* Occasional proliferative inflammatory lesions were found in the interstitial tissue with consequent atypical regeneration of epithelium, but as a rule there was little evidence of metallaxis, the architecture of the organ remaining normal. All types of casts were present except blood casts and those of the broad renal failure type.

Pyogenic Form. All the parenchymatous lesions already described were found with two added and constant changes, namely deposit of amyloid in the glomeruli and along the straight vessels of the medulla, and the occurrence of definite and often severe inflammatory changes in the interstitial tissue. The latter consisted of dense round cell infiltration between the tubules and inflammatory proliferation of collagen and scar formation.

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* Arteriosclerosis with more or less involvement of the renal arteries may of course be present in any kidney and in this way sclerotic vessels are occasionally seen in abnormal kidneys where they have no significance.

Atypical regeneration of tubules accompanied these changes and there had resulted a moderate alteration in the architecture of the kidney. Sclerosis in arteries was often present though usually moderate. All types of casts were present except broad renal failure casts and blood casts. It is interesting to note that although hemorrhage occurred from the damaged glomerular tufts, the absence of exudative inflammatory lesions in these regions prevented the consolidation of the red cells to form definite blood casts.

Non-bacterial Form. Mild lesions of degeneration and occasional necrosis in tubular epithelium were present. Occasional simple glomerular damage with leakage of protein and inconstant hemorrhage occurred but no exudative inflammatory lesions were found. The interstitial tissue and the arteries were not affected.

ARTERIOSCLEROTIC BRIGHT'S DISEASE

The summary of the findings in the kidneys of this group must be considered in somewhat more detail for the lesions encountered if not actually more complex in themselves have at least become involved in recent years in considerable uncertainty of theory. At this point we will consider only the facts themselves.

Common to all the cases of arteriosclerotic Bright's disease were two constant features which seemed to bear a direct causal relation to each other, namely sclerosis of the arterial tree and fibrous scarring of the kidney parenchyma. Of almost equal constancy, but varying in degree of intensity and apparent significance there were also found inflammatory processes in the interstitial tissue and glomeruli and degenerative changes in the tubular epithelium. As a result of the varying admixture of these four processes, vascular sclerosis, fibrosis, inflammation and degeneration, a variety of histological pictures presents itself which might become almost indefinite in its permutations if one considered minute differences as a basis of subdivision. At a later point the problems of classification which thus arise will be considered.

In about one-half of the cases of arteriosclerotic Bright's disease in our series the arterial sclerosis was of moderate degree and the kidney lesions only moderately developed. The disease in the kidney was in a sense incidental, and death resulted from other causes than renal failure. The lesions consisted of a moderate fibrous thickening of the intima of the larger arcuate arteries along with more or less hyperplastic tissue formation. The smaller interlobular arteries were also occasionally involved, here the thickening being more of a diffuse fibrosis of the entire vessel wall, but the smaller arterioles rarely showed significant changes. As a result of this mild arterial involvement the atrophy of the kidney parenchyma and consequent development of fibrous scars was moderate. Inflammatory lesions were limited to those of the subacute type consisting of round cell infiltration and fibroblastic proliferation and these changes were found only in the scars, around the sclerotic arteries and practically never in the glomerular tufts. Degeneration of the epithelium varied in amount depending as it does on incident infections or to passive congestion which may complicate the individual case. Casts of all sorts were present with the exception of blood casts and renal failure casts. Kidneys in which such a histological picture was found were not reduced in size and showed only moderate scarring of their surface. (Plate LX A.)

In about one-fourth of the cases these same lesions in the same relative predominance one to the other were observed, but all increased to an extreme degree. In fact so much of the kidney substance was destroyed that kidney failure resulted and death from uremia ensued. The sclerosis of the arteries was marked and extended down through the interlobular arteries into the arterioles and so into the tufts of the glomeruli. These structures as well as the tubules were atrophied and fibrosed by the irregular and extensive development of scar tissue. Epithelial degeneration, in part the result of the irregular local congestion of the tissues which had developed from the irregular obliteration of veins and the capillary bed, was often marked. Inflammatory lesions, though more marked than in the mild form of the disease, were still confined to the scars and adventitia of the sclerotic arteries. The glomeruli remained as a rule entirely free. As a consequence of all these changes a considerable alteration of the architecture of the kidney was produced, resulting in the patchy metallaxis which is so typical of the terminal stage of hemorrhagic Bright's disease. Beside hyaline, epithelial and granular casts, broad renal failure casts were present. (Plate LXXII A.)

In the final fourth of our series of cases the same essential lesions of arteriosclerosis, fibrosis, inflammation and degeneration were again found. But the lesions, especially those of inflammation, were much more active. About the sclerotic vessels and throughout the fibrous scars leucocytic infiltration was much more intense and among these inflammatory cells could be found polymorphonuclears. Even the glomeruli were not spared the inflammatory involvement, though acute exudative inflammatory changes, such as the pouring out of fibrin, hemorrhage or the formation of crescents in Bowman's space were never observed. Just as these inflammatory lesions were markedly active and intense in degree, so were the sclerotic changes in arteries. The fibrous thickenings, at least in the smaller vessels, had almost the appearance of coagulated exudate while necrosis of their entire walls could even be found. Epithelial degeneration was also correspondingly increased in amount and intensity and resulting cast formation was prevalent, but no blood casts were found. In none of these cases were the kidneys so damaged as to fail, and death was due to arterial accident. (Plates LXVIII A and LXXXIV.)

This is not the time to interpret the significance of these findings, but for future reference we would emphasize that the same lesions were found in all the cases, the differences being simply those of intensity and degree of activity. In Table XLV the individual cases are grouped in their proper order.

Table XLV
Arteriosclerotic Bright's Disease

	Age	Death from	Degree of lesion	Amount of inflammatory involvement	Remarks
LX. Leonard C.	35	circulatory failure	slight	insignificant	
LXII. Kenneth G.	39	circulatory failure	slight	insignificant	
LXIV. John H.	80	pneumonia	slight	insignificant	
LXVII. Jane M.	45	cerebral hemorrhage	slight	insignificant	
LXIX. Tod P.	49	circulatory failure	slight	insignificant	
LXIII. William G.	55	circulatory failure	moderate	slight	blood urea 110 mg. occasional renal failure cast
LXVI. William L.	45	circulatory failure	moderate	moderate	blood urea 207 mg. many renal failure casts
LXXII. Samuel S.	44	circulatory failure	marked	slight	many renal failure casts
LXV. Martha H.	36	uremia	marked	moderate	
XLV. John W*	42	uremia (apoplexy)	marked	moderate	
LXI. Edward G.	24	?	moderate	marked	
LXVIII. Edward P.	57	circulatory failure	moderate	marked	
LXX. Joe R.	43	?	moderate	marked	History of lead poisoning

* Considered terminal hemorrhagic Bright's disease by Clinician.

Chapter X

A THEORETICAL DESCRIPTION OF THE COURSE AND SEQUENCE OF THE PATHOLOGICAL PROCESSES IN BRIGHT'S DISEASE

CHAPTER X

A THEORETICAL DESCRIPTION OF THE COURSE AND SEQUENCE OF THE PATHOLOGICAL PROCESSES IN BRIGHT'S DISEASE*

To this point the reader has doubtless been struck by the peculiarly disconnected and halting arrangement of our descriptions of what we have observed in the kidneys of the various forms of Bright's disease that the Clinician had established by his methods of examination. But this, in part at least, was the result of a deliberate intention, for we had no desire to introduce our study by any "molding of isolated facts into a comprehensible whole," but rather to present clearly the facts concerning which we feel there should be little disagreement.

Interpretation of facts is, however, one of the necessary functions of the pathologist, so that in what follows we have arranged the data of our observations in the order and succession that has appealed to our scientific imagination. Obviously the course of our speculation has been influenced by and follows closely that of the men who established the modern theory of renal pathology. But even considering this substantial support, it must be kept in mind that what we are describing now is to be regarded as the result not of observation or experiment, but of ratiocination and imagination.

In degenerative Bright's disease a toxic agent† reaches the kidney by way of the blood stream and is distributed throughout its tissues. There

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* J. O.

† In many cases since the "toxic agent" is a well-defined substance which may be introduced experimentally into an animal's blood stream this expression is an entirely legitimate one. In certain instances, however, the term is merely the expression of an analogy which is based on the perhaps perilous assumption that like effects must be the result of similar causes. In our series of degenerative Bright's disease the term is used in its strict and proper sense when applied to the explanation of the non-bacterial group, and, judging from experimental evidence, to the pyogenic series as well, though here the "toxic sub-

results, judging from the findings of experiment, a prompt response on the part of certain elements of the kidney, notably the tubular apparatus and to a lesser degree the glomeruli. As Ophüls[56] has shown, within twenty-four hours of the injection of small amounts of certain heavy metals morphological changes may be found in the finer elements of the epithelial cells of the convoluted tubules. But this morphological reaction is not the first response of the kidney to the toxic irritant, for some hours before their appearance, functional disturbances may be noted. Throughout those portions of the tubules which experimental evidence has shown to be the most susceptible to damage, that is the convoluted segments and the broad ascending limbs of Henle's loop, there appear all those lesions which we have grouped as degenerative. Depending on the nature of the toxin, its concentration and to a certain extent on the length of time it affects the kidney there occurs cloudy swelling, fatty degeneration or finally necrosis and as a result of these changes the tubules are filled with detritus. The detritus may remain more or less unorganized but in the lower reaches of the tubules it is in great part consolidated into definite casts.

Concomitantly with these tubular lesions the glomeruli have suffered. Morphological changes in their tissues are not striking, but the fact that they are no longer normal is readily seen in the observation of protein leakage through their membranes and occasional fatty degeneration or even necrosis in the cells of their tufts.

Such may be considered the course of the early phase of the disease. Various eventualities may now follow. If the toxic substances cease to reach the tissues, reparative changes may occur which replace the destroyed elements in a complete manner and in their original form. Such a kidney,

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stances" have not been isolated. In the cryptic group, however, its use is merely a conveniently hypothetical makeshift which may be used until we can speak more intelligently from fact.

as has been proved by experimental procedures, is indistinguishable both morphologically and functionally from the normal organ.

On the other hand if the toxic substances remain in the circulation, the process of degeneration continues but the appearance of the lesion throughout the kidney is complicated by regenerative and reparative changes. So for a considerable period of time this tearing down and repair of the kidney structure may continue without any great departure from the original architectural plan of the organ. In certain cases, however, proliferative changes of an inflammatory nature begin to appear in the interstitial tissue of the kidney. There is an increasing development of connective tissue between the tubules accompanied by the collection of focal areas of round cell infiltration. These changes may be found in any of the subgroups of degenerative Bright's disease that extend over a sufficient length of time, but they are particularly well marked in the pyogenic group where they are associated with amyloid deposition. Here the round cell infiltration and the connective tissue proliferation is extensive, and may be followed as time goes on by a certain amount of contraction of the kidney.

Along with this development of the connective tissue there goes a change in the type of regeneration of the epithelial elements. We have already mentioned the association of atypical epithelial regeneration and fibrosis in the experimentally produced disease. As a result of these processes in both the parenchyma and connective tissue framework the architecture of the organ in the later stages of the disease begins to change from its original plan. The obliteration of glomeruli and collapse of tubules along with the development of extensive and at times retracted scars, all combined with alterations in the vascular supply of the kidney, may produce the typical structure if not the marked reduction in size that is characteristic of the "contracted kidney."

This mixture of productive inflammatory lesions and parenchymatous degeneration, which is so well marked in the pyogenic group, is of especial interest since in it we have a form of Bright's disease in which degenerative and inflammatory lesions are as a rule of equal degree and extent. Most certainly they are of equal importance, both clinically and pathologically, in the course and outcome of the disease so that the group forms in this sense a condition which really lies midway between what has been called "nephritis" and "nephrosis" and which cannot properly be described by either term.*

It may be that etiological factors are the cause of this intimate relation between the two tissue reactions of inflammation and degeneration. It is suggestive certainly that the toxic substances that are the most frequent cause of degenerative epithelial changes in the kidney in man, namely products of bacterial activity, are those which typically produce inflammatory reactions in all tissues, and that the complicating inflammatory changes of the so-called "nephroses" are most marked in the pyogenic group which is definitely the result of infection. The amyloid infiltration which is so commonly associated with the degenerative and inflammatory changes cannot, as we have previously stated, be the cause of the latter. *A priori* this relation between the two types of changes found in degenerative Bright's disease is exactly what one would expect from an etiological factor of bacterial infection. Experimentally it is true that the production of these lesions by such means has not been entirely successful though in the experiments of Bailey[58] the conditions were closely approximated, but this may be explained by the difficulty in reproducing experimentally the long-continued time element that usually exists in spontaneous infections in man rather than to differences in the reaction of the kidney itself.

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* The experimentally produced disease which follows uranium intoxication to which we have previously referred is an even more remarkable link between "nephrosis" and "nephritis." In its earliest stages it resembles very closely the lesion which follows the administration of other heavy metals, notably corrosive sublimate which is usually considered the "nephrosis" *par excellence*. The minor differences which have been described between the two intoxications seem to be only those in degree not of the nature of the lesions.[57] Yet in its late stage the inflammatory processes are so marked as to cause contraction of the organ. Apparently a disease, originally a "nephrosis" has become a "nephritis."

Bacterial infection is of course not the only cause of inflammatory lesions in the kidney. That they may also result from poisonous substances other than those of such an origin is clearly shown by the experimental production of chronic inflammatory lesions in animals by uranium intoxication. And here again is found the same double effect of a toxic substance in producing both types of reaction in the kidney, for this chemical substance causes extensive parenchymatous degenerative changes as well as proliferative lesions. Then too the assumption of the hypothetical "toxic substance" required for the explanation of the etiology of the cases of our cryptic group is another similar example of the twofold effect of an irritant or some other abnormality in the blood stream. In one of these (Plate LXXVII) both inflammatory and degenerative processes were present. It is in this group that would be included we suppose such nephroses as Ebstein[59] and Wolbach[60] have described and in which Bell[61] has recently emphasized the importance of the admixture of inflammation. These we shall not discuss for neither our clinical or pathological observations have disclosed examples of them.

We see, therefore, that in degenerative Bright's disease there are associated degenerative and inflammatory processes and that though the former may prevail to such an extent that one is justified in stating that no "significant" inflammatory lesions are present, such do occur in many cases and that in one group, the pyogenic, the inflammatory reactions are of almost equal degree to those found in forms of Bright's disease where, with a similar etiology, they are the prevailing picture. Quantitatively these conditions may be separated by the reactions in the tissues; qualitatively, the essential processes are similar.

Table XLVI

Course of Pathological Processes in Degenerative Bright's Disease

Degenerative Bright's Disease

← *Cryptic*	↓ *Pyogenic*	→ *Non-bacterial*
	All associated with deposition of amyloid in glomeruli and medulla.	
1. Degeneration. All forms of regressive change in epithelium of convoluted tubules and broad ascending limbs of Henle's loop. Cloudy swelling, fatty degeneration, necrosis and desquamation. Hyaline, granular and fatty casts. Increased permeability of glomerular membrane, pyknosis of tuft cells.	1. Degeneration. All forms of degenerative processes. "Severe form" of cloudy swelling, fatty change and necrosis and desquamation in convoluted tubules and Henle's loop. Casts of granular, fatty and waxy type. Glomerular hemorrhage the result of simple damage not of any exudative inflammatory process.	1. Degeneration. All forms of regressive processes including necrosis and desquamation in tubular epithelium with corresponding cast formation. Simple glomerular damage with protein leakage and pyknosis of tuft cells. Regeneration of normal type.
2. Sclerosis of arteries. Insignificant.	2. Sclerosis of arteries. Present but not severe and affecting only larger branches.	2. Sclerosis of arteries. None.
3. Inflammation. Insignificant. In all cases, regeneration of normal type with complete restitution of kidney structure. In certain cases mild proliferative inflammatory changes in interstitial tissue with development of fibrosis and associated atypical regeneration similar to experimental uranium nephritis. (Case L.)	3. Inflammation. Diffuse productive inflammatory processes throughout interstitial tissue with resulting fibrosis and round cell infiltration. Considerable atrophy and distortion of tubules as a result, with atypical epithelial regeneration.	3. Inflammation. Insignificant or absent. (Here would be included the sublimate kidney.)

In hemorrhagic Bright's disease a poisonous substance also reaches the kidney tissue but here more is known of its nature, for clinical, pathological, and in a lesser way experimental evidence has accumulated which connects the disease with streptococcus infection. The reader is referred to a recent discussion of this problem by Longcope.[62] That we are dealing with the effects of a "toxin" is fairly certain from the fact that repeated attempts to demonstrate the streptococci themselves in the tissues of the kidney have failed. Different suggestions have been advanced to explain their absence. Ophüls has suggested that although the organisms do reach the glomeruli by the blood stream they are immediately lyzed by some process in the capillary loops of the tuft. This would perhaps explain the violence of the inflammatory reaction in the glomeruli in this type of Bright's disease, for such a mechanism would doubtless liberate a high concentration of toxic substances in the confined area where the lesion is so pronounced. Perhaps some local sensitization of the kidney tissues to the bacterial products plays a part in the tissue reaction. These theories however still await definite experimental confirmation.

Whatever the exact mechanism may be the irritating substances reaching the kidney by the arterioles are thrown into the capillary bed of the glomeruli and produce a violent reaction. Such a reaction will of necessity from the nature of the tissue involved be chiefly an inflammatory one. The capillaries are dilated, leucocytes are extruded, protein leakage occurs and even thrombosis and necrosis may result. Those elements that, from their anatomical structure and nature, may respond by degenerative changes, do so. Fatty degeneration or even necrosis is found in the endothelial cells of the tuft and the rudimentary epithelium of the capsular space. The inflammatory process continues. Bowman's space is filled with exudate so that crescents form in the extracapillary type of the lesion or if the process is more or less contained within the tuft, the intracapillary form of glomerulitis results. In the meantime the toxic substance has reached the tubular epithelium. Since the blood has previously passed through the glomerular capillary bed and has produced there the violent reaction we have described, it is possible that its toxic properties have been reduced before it reaches the epithelium. It may be on the other hand that these poisonous substances have been excreted through the glomeruli and reach the epithelial cells only by absorption from the lumen of the tubule. At any rate there occurs as a response to them the only morphological reaction of which the epithelium is capable, that is, degeneration. The degree may vary from a just visible cloudy swelling to fatty degeneration or even necrosis with desquamation.

The association of these degenerative changes in the epithelium with the inflammatory processes in the glomeruli is nothing to be wondered at. In fact, it would seem almost impossible to conceive of the absence of either of these types of reaction if one considers the fact that bacterial toxins are flooding the kidney circulation, and thus reaching every element of the renal unit. Either process is certainly as true a part of the reaction of the kidney to the toxic substance as the other. Different tissues, glomeruli and tubules, have responded in their own way to the irritant and there is no need to think of any interrelation or dependency of one process upon the other.

The variation that is found in hemorrhagic Bright's disease in the degree of these epithelial reactions is not surprising when one considers the great variations which may occur in the amount of "toxin" or its concentration in the blood stream as it reaches the kidney or as these factors may change as it is distributed throughout the kidney. Both the inflammatory and degenerative lesions as they develop may alter these factors so that again one would expect irregularity of occurrence and distribution in the epithelial lesions. On the other hand since the glomeruli receive the blood first and directly from the arterial supply a comparative constancy in reaction would be expected in them.

The interstitial tissue of the kidney as well is affected by the bacterial poisons, and its response again is determined by its anatomic peculiarity. Inflammation is the striking lesion, though here too degeneration or even necrosis may occur in its constituent cells. But these changes are always insignificant as compared to the hyperemia, edema, and the exudation of leucocytes which characterize the early stages of the inflammatory process. The tubules may be actually separated by the accumulations which occur between them and the whole kidney may become tense and swollen within its capsule. To these exudative inflammatory phenomena are soon added the productive changes of the inflammatory process and none of our cases has been so early as not to show them. They consist of proliferation of fibroblasts, the development of collagen fibrils, at first in delicate form, and the accumulation of "round cells" such as lymphocytes and plasma cells. The distribution of this involvement may be diffuse, the processes extending throughout the entire cortex, or it may be patchy, so that groups or clusters of tubules and glomeruli remain more or less free of the more severe lesions.

Such are the earlier phases of hemorrhagic Bright's disease in its initial and active stages. What may next happen has been shown by the clinical observations which were able to follow the morphological changes in the kidney by means of changes in the urinary sediment. The detailed descriptions of the correlated clinical and pathological findings that we have already given has allowed the reader to judge as to the validity of these methods.

One outcome that may result is a gradual recession of the activity of the process, the disease passing into the latent stage described by the Clinician. Several such cases in our series came to autopsy as a result of death from other causes than renal failure. It is the simpler of these cases of which we shall speak here, omitting the embolic case which was associated with bacterial endocarditis. In the former there were still present active lesions of both inflammatory and degenerative nature. These processes, however, were greatly reduced in intensity so that a search was necessary to find glomeruli in which definite active inflammatory changes were present. Scattered through the interstitial tissue were found small areas of leucocytic infiltration with some slight early development of connective tissue. The epithelial degenerative lesions were also slight. In one case the lesions might almost be considered arrested (Plate XVIII A) though the kidney showed evident traces of earlier damage in the form of recent scars, round cell infiltration and glomerular fibrosis, while in other cases the lesions though rare were slightly but definitely progressive. The irritant was evidently still reaching the kidney therefore, since the reaction of the tissues was continuing and, as is shown by the clinical course of other cases which ultimately ended in terminal hemorrhagic Bright's disease, might at a later time have flared up and the processes continued their destructive course.

After such a period of latency the processes may pass back again into an active stage and this recession and exacerbation of the activity of the lesions may be repeated several times. As the disease progresses by these irregular and halting steps the proliferative inflammatory processes accumulate in their effect. A considerable portion of the kidney is irreparably destroyed and replaced by inflammatory connective tissue so that metallaxis of the organ becomes prominent. It is at this point that the importance of the manner of distribution of these processes, whether diffuse or patchy, becomes evident for this factor determines largely the future course of the disease's development. If the destruction is of the diffuse type it may conclude the history. Uremia is not uncommonly the termination of hemorrhagic Bright's disease while it is still in its active stage, and the failure of the kidney is patently the result of this diffuse type of destruction of its parenchyma. Other individuals, in whom the diffuse involvement though present is still insufficient to produce kidney failure, may die of infection or some circulatory complication, and yet others, in whom the active lesions are patchily distributed and who therefore have considerable renal parenchyma preserved continue their course and the disease passes into the terminal stage which is certain to end in kidney failure.*

The actual lesions which are occurring in this terminal stage of the disease are a continuation of those we have just described. Inflammatory processes in the glomeruli and in the interstitial tissue proceed, becoming as time passes less acute in activity as the later phase of the process produces collagen fibrils. The glomeruli are obliterated and fibrosed and a resulting collapse of the tubules from inactivity occurs. In the interstitial tissue the cellular infiltration and connective tissue formation continues, compressing tubules and glomeruli as it increases, until large areas of the kidney substance are reduced to a tissue that is almost entirely fibrous. Along with these inflammatory processes go the usual degenerative changes in the epithelium, irregularly distributed and varying in amount from time to time in the course of the disease. The arteries as well undergo striking changes. Sclerosis, not only of the larger branches of the renal artery, but also of the smaller arterioles occurs, often to a degree comparable with that seen in arteriosclerotic Bright's disease.

We have already called attention to the transformation that the architecture of the kidney undergoes as this tearing down and building up continues to the development of a patchy metallaxis. This is the most striking phenomenon of the terminal phase of the disease and is the characteristic which not only distinguishes it morphologically from all other stages of this type of Bright's disease, but which sets it apart from all the other forms of the disease as the one which specifically and peculiarly affects the renal mechanism. For as a result of it the outcome of the disease is determined; that is, loss of function and kidney failure with death in uremia. It is an impressive fact that in the earlier stages of this form of the disease, although inflammation and degeneration are much more intensely active, the kidneys are as a rule able to carry on in some manner, provided the accompanying fibrotic inflammatory involvement is not too diffuse, and when death occurs it is due to some other factor than a renal one, often the original infection which is the cause of the kidney damage. And a further confirmation of this dependency of renal failure on metallaxis is found in other types of the disease, particularly in arteriosclerotic Bright's disease. In it the kidney functions remarkably well in most cases and the individual succumbs to some vascular accident, while in the occasional instance where death is due to uremia, a patchy metallaxis with transformation of kidney architecture of a similar character and degree to that usually found in terminal hemorrhagic Bright's disease is regularly found.

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* Case xv is an interesting example of an active hemorrhagic Bright's disease with patchy distribution of the inflammatory lesions which was thrown into a condition of renal failure prematurely by the added strain of an incidental dehydration. Without this accident, judging from the extent of the renal lesion, he might well have survived and passed into the terminal stage of the disease.

Not only the kidney parenchymal units are involved and transformed in the process, but also the vascular bed, both arteriolar and venous. The complicating factors introduced by this change in vascularity we have also described in a previous chapter. Certainly as Baehr and Ritter have recently emphasized, these vascular changes must play an important part in affecting the changes which are occurring throughout the kidney. They too must be considered an important factor in the histiogenesis of the disease and one that cannot be ignored in any scheme of classification.

So the processes continue until a point is reached when the "kidney," if we may still so call this organ whose glomeruli, tubules and vessels have been entirely rebuilt in a haphazard and apparently planless manner, is no longer able to perform its excretory function and fails. Not only is this a failure of nitrogenous secretion, but the failing organ can no longer free itself of detritus in a normal manner and broad renal failure casts form in the ducts of Bellini and appear in the urine. The kidney, perhaps only a tenth its original volume, is no longer sufficient and so death results from uremia.

The description of the course of the degenerative and hemorrhagic forms of Bright's disease is, compared to what confronts us now, a comparatively simple matter. In them toxic substances reach the kidney by the blood stream and affect the tissues directly. In arteriosclerotic Bright's disease another step is commonly assumed to appear in the chain of events. Something affects the arteries and the change in these affects the kidney tissue.

Our discussion is limited specifically to the *renal* lesion in Bright's disease, and if one accepts the statement that Gull and Sutton[63] made in 1873, namely that this type of the disease is a "general morbid change of which contraction and atrophy of the kidney is part and parcel," we would be freed of the involved discussion of why or by what method the arteries of the kidney are involved. Unfortunately, though we believe the dictum we have just cited to be essentially true, we also feel that there is more to be seen in the kidneys of this form of disease than can be covered by the simple conception of atrophy from decreased blood supply, and this complicates our hypothetical description of the course of the process. In the next chapter we shall describe the conceptions of other writers concerning these processes and their relation one to the other, and may proceed for the present to an exposition which, though arbitrary in its manner, will at least serve as an introduction to our later discussion.

From a combination of factors, notably mechanical strain and what for want of a better name we may call senescence, the arteries of the body as a whole develop abnormalities which can be grouped together as "arteriosclerosis." These lesions need no description at the present time. Certain arterial beds, for reasons not entirely clear but which need not immediately concern us, suffer more than others and among these is that of the kidney.

TABLE XLVII

COURSE OF THE PATHOLOGICAL PROCESSES IN HEMORRHAGIC BRIGHT'S DISEASE

Initial Stage (no cases)

Active Stage ⇄ Latent Stage

Active Stage

1. Inflammation.

Acute exudative and early productive processes: intracapillary and extracapillary glomerulitis, hemorrhage and collection of exudate in Bowman's space, edema and leucocytic infiltration of interstitial tissue. To these soon added proliferative processes in both glomeruli and interstitial tissue.

2. Degeneration.

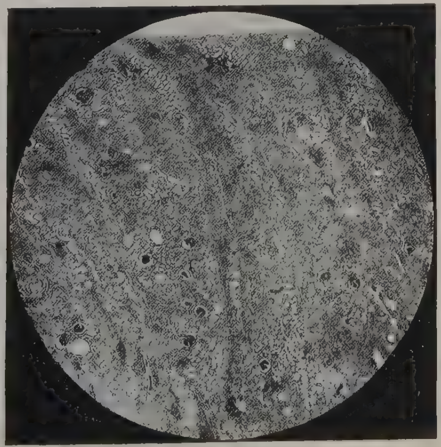
Variable in degree, usually marked, affecting convoluted tubules and ascending limbs of Henle's loop. All stages from cloudy swelling, fatty degeneration to necrosis and desquamation. Casts of all sorts except renal failure in tubules.

3. Sclerosis of arteries.

Slight, increasing with time.

These processes distributed so as to produce metallaxis of

Diffuse Type or Patchy Type; unless interrupted by some extrarenal accident these survive, passing on to



death from uremia

Latent Stage

All lesions of active stage but at low degree of activity. Considerable search required to demonstrate glomerulus with inflammatory involvement or hemorrhage. Epithelial degeneration only slight. Healed scars of former lesions.

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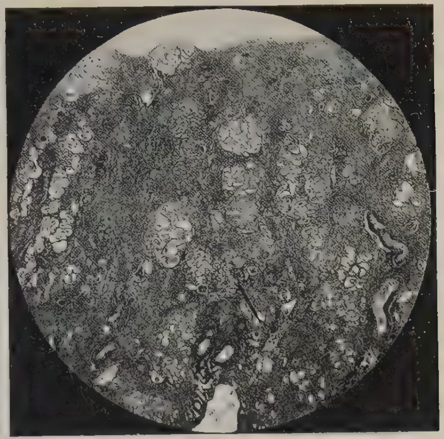
Healed

Complete arrest of all processes with scar development. Only 1 case (Case XVIII) approaches this condition.

Terminal Stage.
Characterized by extreme metallaxis of patchy type and renal failure.



1. Inflammation.

Traces of acute processes in glomeruli and interstitial tissue, but characterized by subacute and chronic proliferative lesions in these regions. Patchy fibrosis with destruction of cortical tissue which leaves islands of comparatively less affected glomeruli and tubules.

2. Degeneration.

Extreme degree of all types often occurring in irregular periods. As a rule patchy in distribution leaving areas of comparatively normal tubules, or regions where atypical regeneration is observed. Atrophy and distortion of tubules by inflammatory fibrosis. Casts of all sorts, especially renal failure casts in ducts of Bellini.

3. Sclerosis of arteries.

Increasing to marked involvement not only of larger arteries but also of arterioles.

There seems to be no doubt that, added to the causative factors already mentioned, which from their nature will be operative in every individual and which may therefore be considered as constant, are other factors which, variable in a sense in their occurence may add their effect in certain cases. Among the most important of these is a toxic factor. Some of these toxic products are definitely known, such as lead, those accumulating in the blood stream in gout, and, as Ophüls has emphasized, those derived from chronic sepsis.* The last named seems to be by far the most frequent.

We, therefore, may take for our description of the course of an arteriosclerotic Bright's disease an individual whose arteries have suffered to a greater or lesser degree from what we have called the constant factors of arteriosclerosis. One of the variable or auxiliary factors is now introduced, a chronic infection of low degree of activity for example. Toxic substances gain the blood stream from this focus and reach the kidneys, and there occurs an acceleration of the arteriosclerotic processes in the vessels. There results an increased fibrous thickening of the intima of the larger arteries and a proliferation of elastic fibers. The lumen of the vessel is reduced as the process extends down into the interlobular branches so that they now stand out in sections of the cortex, greatly thickened and tortuous. Whether there is an actual spread of these changes from the larger to the smaller of these vessels may be doubtful, but at least the smaller branches are still relatively well preserved when the larger arteries are definitely diseased.

Eventually the afferent arteriole is affected and the process may be followed into the capillary bed of the glomerulus. This is gradually obliterated by the development of collagen around the thickened and collapsed capillaries. Necrosis, apparently from vascular obliteration, may also be found in the glomerular tuft.

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* The etiological importance of lead and gout are illustrated in our series by Cases LXX and XXXVI. In the former inflammatory lesions were a striking part of the renal lesion, the process evidently corresponding to Volhard and Fahr's "malignant sclerosis." In the latter, the original etiological factor was obviously a tonsillar infection and the renal lesion which developed a hemorrhagic Bright's disease. The latter development of gout with urate deposit in the kidney may have been responsible for the extreme vascular sclerosis that was found in the end.

Changes are also observed in other tissues of the cortex. Tubular collapse, the result of an inactivity atrophy following the glomerular obliteration, occurs, and along with this a proliferation of the intertubular connective tissue. The result of this, combined with the glomerular destruction, is the development of scars in the cortex which may be seen in sections to be closely related to the obliterative lesions in the vessels. So the processes continue. Kidneys may be found in which a few scars are seen scattered through the cortex and others in which the cortex and even medulla are diffusely infiltrated with connective tissue so that they are as a result considerably reduced in size. These are the "genuine" or "primary contracted kidneys" that were formerly considered the results of a chronic "interstitial" nephritis.

So far our description may be well summarized by Fahr's words as an "anemic atrophy." In many cases, however, where the marked structural changes of a "contracted kidney" are approached in degree, processes are observed which can hardly be described by this term. The most striking of these are inflammatory changes both in the interstitial tissue and to a lesser degree in or around the glomeruli.

We have just described the collapse of the tubule from inactivity atrophy and the proliferation of connective tissue about it, and there seems little doubt that a considerable amount of the scar tissue develops in this comparatively simple manner. In the larger and more diffuse scars, however, definite evidence of inflammatory connective tissue proliferation is always found. The fibrous tissue, rich in collagen fibrils, is heavily infiltrated with inflammatory leucocytes, such as lymphocytes and plasma cells. In the most active cases even polymorphonuclears may be found by careful search. This inflammatory proliferation of connective tissue between the tubules is therefore in every way comparable to that observed in other forms of Bright's disease, and there is no doubt in our mind that in many cases it plays an equally important part in the outcome of the disease. In the glomeruli as well, beside simple atrophic and fibrotic changes, inflammatory lesions are not infrequently found, particularly in tufts in which necrosis has occurred as the result of vascular obliteration. Such processes are mild, however, being limited to a moderate infiltration of leucocytes. (Plate LXXXIV.)

Epithelial degeneration also frequently occurs in arteriosclerotic Bright's disease often in peculiarly intermittent periods that may be of such severity as to mislead the clinician who is following the kidney lesions by means of the changes in the urinary sediment. It is conceivable that such damage is the result of the same toxic substances, the auxiliary factors previously mentioned, that are affecting the blood vessels and that is causing the inflammatory lesions, or it may be the result of congestive phenomena, caused in turn by either a failure of the general circulation or by those local congestive processes limited to the kidney which are the result of vascular obliteration by scar tissue development.

Our conception of the course of arteriosclerotic Bright's disease depends therefore on the assumption that added to the constantly occurring factors which produce arteriosclerosis is an added factor, which may not only accelerate the vascular lesions and thus damage the kidney, but in all grave cases of this type may affect the organ tissues directly in exactly the same manner and with much the same effect as is observed in hemorrhagic and in degenerative Bright's disease.

All these processes continue. The architecture of the kidney, as in the terminal stage of hemorrhagic Bright's disease, undergoes a profound change and a patchy metallaxis develops. The kidney is reduced in size (primary contraction) and may in the end become insufficient so that renal failure results. In most cases, however, the picture is completed long before this event occurs by the intervention of an arterial accident in some other vascular bed, such as a coronary occlusion or a cerebral hemorrhage.

The picture which we have described is the typical one for arteriosclerotic Bright's disease and from it the lesion found in any individual case may differ considerably. But these differences are only in degree of intensity, acuteness or extent of involvement. In some the lesion in the kidney may be looked upon as merely incidental to the general vascular disease which ends by cerebral or circulatory complication. In others the processes, though still slow in their development, eventually end by destroying sufficient renal tissue to produce uremia. And finally there is that important group in which the lesions of sclerosis of the arteries, degeneration and inflammation are acutely active. It is the inflammatory involvement in this final group which has most impressed recent investigators and caused so much discussion in the theory of the disease. But the degenerative and the sclerotic lesions are equally violent in these cases, so that the impressiveness of the inflammatory processes seems to come more from astonishment at their occurrence, conflicting as their presence is with established theory, than from any reason actually inherent in the process itself.

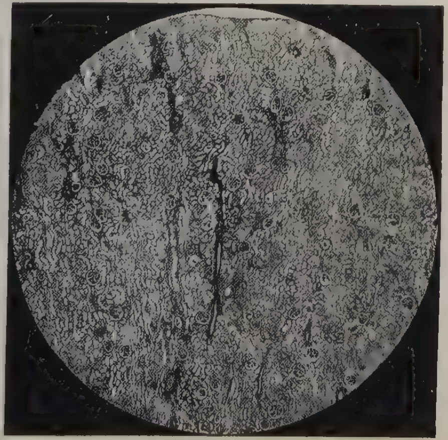
Such briefly is the course of the various forms of Bright's disease as we conceive them. Inflammation, degeneration and vascular sclerosis are all present in all forms of the disease. And how could such a combination of reactions be avoided if any toxic element or any change in the entire environment of the organ by alteration in its blood stream plays a role in the etiology of the disease? What could prevent the diffusion of irritants through the tissues of the organ and limit their effects to changes in glomeruli or in tubules or in vessels? And why should the response of any two of these elements be ignored while the third is made the basis of the theory and

TABLE XLVIII

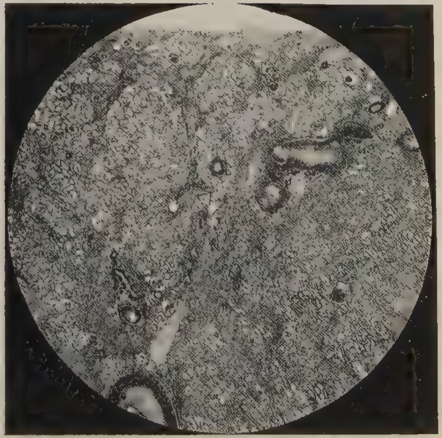
COURSE OF THE PATHOLOGICAL PROCESSES IN ARTERIOSCLEROTIC BRIGHT'S DISEASE

Arteriosclerotic Bright's Disease

Mild
(appearing often as incidental part of general arterial sclerosis)



Severe



1. Sclerotic lesions.

Moderate, increasing in degree, in larger arteries. Smaller arterioles only slightly affected. Anemic atrophy of parenchyma also moderate with development of fibrous scars.

2. Degeneration.

Slight to moderate. Often related to congestive phenomena of failing circulation.

3. Inflammation.

Slight, limited to round cell infiltration of fibrous scars in interstitial tissue.

Unless death from circulatory failure or incidental infection may continue to a later stage of

renal insufficiency

↓

1. Sclerotic lesions.

Moderate to extreme, involving both larger vessels and arterioles and glomeruli; arteriolar and glomerular necrosis. Extensive fibrosis throughout cortex with destruction of parenchyma.

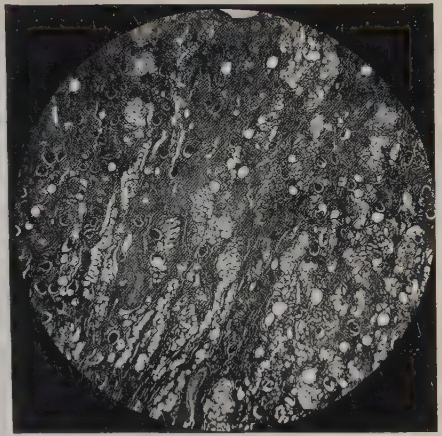
2. Degeneration.

Varying in degree, usually marked and of all types including necrosis of epithelial cells. Hyaline, granular and fatty casts.

3. Inflammation.

Pronounced in interstitial tissue and occasionally in glomerular tufts. Processes usually proliferative, but occasional exudative changes found.

These processes usually interrupted by some accident before development of renal insufficiency.



1. Sclerotic lesions.

Extreme, involving not only larger arteries but also arterioles of cortex and extending into glomerular tufts. Widespread atrophy of parenchyma with extensive fibrosis and consequent reduction of cortex. Development of patchy metallaxis in kidney structure with islands of relatively uninvolved parenchyma.

2. Degeneration.

Moderate to severe, occurring in irregular intervals, apparently the result of both general and local disturbances of circulation. Often of sufficient degree to obscure clinical findings in urinary sediment. Hyaline, granular and fatty casts as well as renal failure casts.

3. Inflammation.

Increased in degree, but usually limited to interstitial tissue with only moderate involvement of glomeruli. Exudative processes rarely seen, the proliferative type being characteristic, associated with round cell infiltration.

classification of the disease? But these questions, the last in particular, are material for our concluding chapter where an attempt will be made to justify our conceptions of the theory of Bright's disease and its classification not only in the light of our observations but by considering the opinion of some others.

Chapter XI

A CLASSIFICATION AND THEORY OF BRIGHT'S DISEASE

Chapter XI

A CLASSIFICATION AND THEORY OF BRIGHT'S DISEASE*

Grau teurer Freund, ist alle Theorie, Und grün des Lebens goldner Baum.

So completely do these words express the contrast between the facts and theory of our subject, that even considering the dubious character of their exponent and his ambiguous reasons for their pronouncement we cannot refrain from citing them as an introduction to our final chapter. The observation of what is occurring in this disease and the following of its progression to the ultimate catastrophe is a fascinating research, but, for some at least, the regimentation of these multiple and complex facts into an organized scheme which will fit not only their observations but also conflict not too violently with those of others, is an arduous and ungrateful task.

However, as we have said before, such is the duty of the pathologist. The Clinician has established a particular set of pigeon-holes of classification and we must now defend their peculiar advantage as contrasted to those of another set. There is no possibility of considering them in the light of all the various theories that have been proposed, nor to anticipate all the objections that will be raised against them. We shall, therefore, content ourselves with the consideration of only a few of our more obvious difficulties.

If we are to justify our classification, perhaps the first point that the pathologist will be asked to consider is the use of the word "Bright's disease," for apparently the term is under the shadow of some reproach. Volhard and Fahr in their text point out its inadequacy and unsuitability, while Oertel criticises at length its "indefiniteness." Yet "Die Brightsche Nierenkrankheit" and the "Anatomic Histologic Processes of Bright's Disease" are the titles which these authors evidently felt in the end best summarized their work. The term must, therefore, have certain advantages and we believe that from the viewpoint of the pathologist it has many.

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* J. O.

Oertel prefers the word "nephritis" for his classification to that of "Bright's disease" because it has a more definite meaning. And just because the term nephritis has this definite meaning we prefer the term "Bright's disease," for we do not believe that there is a virtue in being definite and specific in the terminology of what is indefinite and non-specific. If "nephritis," the word commonly preferred to it, has any certain meaning it is that of "inflammation of the kidney" and to attempt to cover the multitude of processes that are occurring in the disease by such a meaning is clarification by the method of ignoring facts. The same criticism applies of course to the word "nephrosis." There may be cases where this term is warranted, that is, where there are no significant inflammatory lesions present in the kidney, but such are exceedingly rare.

In the present day the words "nephritis" and "nephrosis" have indeed acquired a certain value in practical usage but this has become possible only by means of mental reservations that have been subconsciously appended to them and which are a denial of their connotation. And these reservations often have sunk so deeply into the subconscious realm of the user's mind that it is doubtful if their importance in any definite conception of what is occurring in the kidney remains. The resulting artificiality of these terms becomes strikingly evident to the teacher of pathology who has the task of initiating students, accustomed to methods of reasonably rational scientific nomenclature, into the theory of Bright's disease. Their reaction to his explanation that "nephritis" is not "nephritis" but often "nephrosis" as well, is quite the rational and proper one. It is only after considerable wandering in the devious paths of nosography that they become reconciled to a passive acceptance of such paradoxes.

"Nephritis" has apparently been endowed with attributes which warrant high consideration. As we have just stated, not only is an acquired mental mechanism needed to make its usage at all possible but the amazing fact stands out that the whole modern conception of pathology concerning the reactions of tissues to abnormal irritations, a field which includes a considerable portion of the science, has been modified by the attempts of its supporters to get these diseases of the kidney into the strict connotation of the word. From Cohnheim's experimental demonstrations of the nature of inflammation down to the present day it is these kidney lesions in particular that have been a stumbling block to those who wish to preserve Virchow's dual conception of the inflammatory process. Aschoff for example would maintain a "parenchymatous" inflammation, since there is evidence that the earlier stages of degeneration in the epithelium are an "active" response to an irritant. The activity of the response is to become the definition of inflammation. Oertel would even include regeneration and hyperplasia of epithelium among the inflammatory processes for similar reasons.

If the conception of inflammation is to be extended in such a manner and by such criteria there are a few vital processes which could not ultimately be included in it. Certain features, especially the proliferative phenomona, have of necessity been added to Cohnheim's original description, but the extension of the concept to include more and more cannot go on indefinitely. Celsus, if not the first to define, at least early described inflammation and Cohnheim rationalized this description by experiment. It would seem to us simpler and more useful therefore, to limit the concept of the process rather than to expand its definition to the point where its value is lost in its all-embracing properties.

There is no need, however, for us to engage in a discussion of the theory of inflammation except as we are concerned with the usage of the term "nephritis." To return to the definitions of parenchymatous inflammation just cited, it would indeed be logical to classify a "sublimate kidney," as a "nephritis," as Oertel does, and thus used the term does not even need the modifying adjective "parenchymatous" which is usually prefixed to it, but our objection to such procedure we have stated. Yet on the other hand we find Ribbert[64] who, admitting the presence of inflammatory processes but believing that dysfunction can be the result only of regressive processes of degeneration, insisting that all types of "nephritis" must be called "nephrosis!"

Evidently the terms "nephritis" and "nephrosis" are "all things to all men" and if the ablest have used them to apply to the same thing with meanings exactly the converse, this fact alone would seem to prejudice their usefulness if any scientific accuracy is desired in nomenclature.

Apart from these theoretical criticisms, but in truth mostly because of them, the meaning of many of these terms has become completely confused in every day usage. Such might have been expected since the greater part of their definition consists of mental modifications of their meaning. "Chronic interstitial nephritis" is fortunately disappearing from modern usage, but when it does persist gives an entirely false picture of the histogenesis of the disease. It bears no possibly conceivable relation to that disease which with some degree of accuracy is called "acute or subacute interstitial nephritis." Other terms have undergone a subtle metamorphosis by which their original anatomical meanings, clear and understandable even if inaccurate, have taken on an ambiguous and indefinite cast, which is vaguely "functional" and clinical in its conceptions. "Chronic parenchymatous nephritis," as Volhard and Fahr have shown, is a term which has so suffered until it now includes a wide variety of conditions. At the present time it is entirely impossible for any reader, no matter how complete his general understanding of the subject, to have any idea of what is meant by this term unless he is familiar with the writer's personal usage in the matter. Nephrosis to many we believe, is largely a matter of edema and abnormal plasma protein ratios rather than the clear picture of any renal lesion. Perhaps these are indeed the essentials of the disturbance, but they bear no relation to the term under which the disease is classified and that only is the matter we are at present considering.

Serious objection may also be raised to the other terms that have been suggested for the disease in the kidney. "Tubular nephritis" avoids none of the difficulties of fact or theory that we have mentioned. It describes only half the picture that is present in the kidney and in a way that suggests an importance for the feature that is named which requires the same mental reservations we have previously mentioned if it is not to be misleading. The processes in all the different forms of the disease that we are considering are "diffuse." "Nephropathy," meaning only "disease of the kidney," covers such a wide field that it fails to specify any particular condition unless encumbered with awkward adjectives.

And so we might continue. The multitudinous nomenclature is the obvious indication of its inadequacy. As we have stated before, when some term must be found to cloak this multitude of nosological sins, it is usually "Bright's disease" that is revived. Why, then, should the term be so rigorously banned when the formal classification of the disease is to be established?

The objection that the term is eponymic may be of importance to editors. The objection that it is not a pathologically descriptive term can be met with the answer that it is entirely impossible to describe such a complex mixture of related conditions as we are considering by any usable term. "Bright's disease" makes no such attempt and moreover has the great theoretical value that it does not limit attention to the lesion in the kidney, which is only a part of the general disturbances that exist. The term has in fact as great pathological or clinical significance as many valuable medical terms; "diabetes" for example. One can picture the confusion if attempts had been made to name this disease by some term based on abnormalities of the pancreas. Degeneration, inflammation and sclerosis might have all been advanced as the distinguishing feature to be recognized in the nomenclature, if the condition had not been known and named long before histological refinements had indicated any suspicion of pancreatic involvement. The analogy between the two diseases in each of which the affection of a certain organ plays the chief role but where general disturbances are of great importance is a remarkably close one. Yet no one would attempt to designate the complexities that can be covered by "diabetes" by such a term as "pancreatitis," though inflammatory processes may play a considerable part in the production of the disease. The dissatisfaction of the immediate proponents of "pancreatosis" and "pancreasclerosis" to any such summary procedure may be readily imagined.

For these reasons we are well satisfied as a pathologist to use the term "Bright's disease" for a system of classification. The various forms or subgroups of the disease as established by the Clinician seem to us to also be as satisfactory from the pathologist's standpoint as can at present be devised. The term "degenerative Bright's disease" emphasizes the significant process of the condition and this is all we can hope to do in any concise and usable word. "Hemorrhagic Bright's disease" describes a prominent and distinctive feature of the pathological processes as well as of the clinical symptomatology and it places no misleading emphasis on either the inflammatory or degenerative features of the disease. The use of "active," "latent," and "terminal" to denote the activity of the processes is a much clearer description of the state of the pathological lesions than is acute, subacute and chronic. "Arteriosclerotic Bright's disease" not only describes the significant pathological lesion but indicates the relation of this form of the disease to the pathological features of the general arterial involvement which is always present to some degree.

By these conceptions, therefore, Bright's disease is in a certain limited sense a unified condition. And this is due to an equally unified factor in its pathogenesis, namely, that it is the response of an *organ* to an alteration in its environment, the blood stream. In its simplest care it is the response to the irritation of toxic substances. Since the organ contains many *tissues*, each with its own peculiar method of response many forms of response are possible. Various combinations can therefore result, depending on the "nature" of the toxin, but in most cases the prevalence of some type of lesion will form a picture which can be given, for the sake of convenience, a distinguishing name. As one would expect, the picture is not always clear cut and differences in interpretation are not evidences of error or misconception on the part of the observer, but an accurate reflection of the complexity of the reaction of a complex organ.

In degenerative Bright's disease beside the prevailing degeneration are found inflammatory processes as well as vascular lesions. In hemorrhagic Bright's disease the striking inflammatory lesions are combined with degenerative changes and the arterial involvement is often extreme, and all these lesions share equally in the production of the metallaxis which is typical of its final and fully developed stage. In arteriosclerotic Bright's disease, degeneration and inflammation are always present to some extent. The concomitant lesions, which are as a rule less pronounced than the prominent one which has been used to designate the particular type of the disease, are not to be thought of as merely present. They play a part in the course of the disease whose importance is limited only by the degree of their development and this is often a considerable one. In terminal hemorrhagic Bright's disease sclerotic lesions of the arteries for example are especially important in the final outcome, while in arteriosclerotic Bright's disease degeneration often complicates the clinical picture, or inflammatory processes determine the end result.

That such combinations of various lesions occur in all forms of the disease has of course been recognized from the time of the earliest investigators. At one period it was proposed to consider all forms of non-suppurative kidney disease as a single entity, and the reaction from this extreme view, ignoring as it does etiological, symptomatological and prognostic differences, has perhaps been too vigorous. Volhard and Fahr in their sharp separation of those forms of the disease which they summarize as "nephrosis" and "nephritis" admit that the latter may be complicated by a "nephrotische Einschlag." In the arteriosclerotic group difficulty in such sharp division becomes so pronounced, however, that there is some disagreement even between the two co-investigators. In their original presentation the establishment of a "combination form" in which upon a "pure" arteriosclerotic lesion was superimposed an "exogenous" inflammatory process in the vessels and glomeruli, has been modified by the later work of Fahr[43] who now distinguishes three distinct types of arterial involvement associated with renal disease. In "chronic glomerular nephritis" (terminal hemorrhagic Bright's disease) the arterial lesion is the direct result of the chronic glomerular lesion. He assumes that the mechanical factor of an added strain upon the arteries of the kidney which are helping "to pump"* the blood through the obliterated glomerular tuft, combined with a toxic component, the original cause of the nephritis, produces the sclerosis of the arteries. A second form of arterial disease is called "pure" arteriosclerosis, in which the kidney does not suffer significantly and which is part of the general involvement of the vessels of the body. Finally there is a third type, originally considered the "combination form" but which Fahr now calls a "malignant sclerosis," in which the change is not the result of a "pure" arteriosclerosis, but in which the lesions in the vessels are the inflammatory processes of endarteritis and periarteritis. Among the etiological factors which may be the cause of this form of arterial disease are lead, gout, syphilis, and possibly alcohol.

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* This conception of the renal arteries "pumping" the blood through the increased resistance of the obliterated glomeruli is a mechanism which frequently appears in theoretical discussion of renal pathology. We have never been able to visualize very clearly the phenomenon from any definitely known physiological experience and are suspicious that a teleological wish fathers the thought.

The attractiveness of such clear cut divisions is obvious. However, they depend for their validity on assumptions which are generally not admitted. Baehr and Ritter and our findings, to cite only two of the more recent investigations, indicate an essential similarity in the arterial lesion in the late stage of chronic glomerular nephritis (terminal hemorrhagic Bright's disease) and in arteriosclerotic nephritis (malignant sclerosis, arteriosclerotic Bright's disease). This similarity is not merely in morphological appearance but what is more important, in the part played by the arterial lesion in the course, development and outcome of the disease. Furthermore Jores, Aschoff, Löhlein, and Ophuls see no significant difference in the lesions of arteriosclerotic nephritis that would warrant its separation into two distinct diseases but, as our observations also indicate, consider the two conditions two phases of the same disease, differing in degree of intensity.

Beside this complex group of related renal lesions there is another suggested subdivision of nephritis which promises to assume an equally confused position in the classification of the disease. This is the group of focal nephritis.* As originally suggested by Volhard and Fahr two types are

* In the early stages of the clinical study cases were seen which conformed perfectly with Volhard's conception of focal or " herd formige nephritis." But when it was found that many patients seen in the initial stage of hemorrhagic Bright's disease (which corresponds with Volhard's diffuse glomerular nephritis) passed later into a condition which was clinically indistinguishable from that of the patients provisionally classed as examples of focal nephritis, doubt arose as to whether the latter really belonged to an independent form of Bright's disease. The doubt increased when chance revealed the typical urinary findings of the initial stage of hemorrhagic Bright's disease, with transient hypertension and even at times a slight edema, in patients who were entirely unaware of the existence of these symptoms, for this experience indicated that an absence of any history of the symptoms peculiar to the onset of hemorrhagic Bright's disease by no means excluded the possibility that in the past they might have occurred. Finally the conclusion was reached that focal glomerular

sharply distinguished, "embolische Herdnephritis" and "herdförmige Glomerulonephritis."

Concerning the first of these there is a general unanimity of opinion as Löhlein[48] and Baehr[49] have clearly established its pathogenesis. Its association with bacterial endocarditis and embolic origin are definite.

In contrast to these well-recognized lesions is the second type of "herdförmige Glomerulonephritis." This is described as a distinctly different disease from the first type, consisting as it does of a focal involvement of the glomeruli of the same sort as is found in the more common diffuse glomerulonephritis, and it bears no closer relation to endocarditis than does the diffuse disease. Clinically its description does not differ greatly from those of focal embolic nephritis.

There is a sharp distinction in the attitude of clinicians and pathologists towards these two diseases. For many of the former, the two types are apparently well established. The pathologists seem less certain not only of the relation of the two conditions to each other and to the common form of diffuse glomerulonephritis, but even as to the existence of one of them. Fahr[35] states (p. 44) of the lesions observed in "focal glomerulonephritis "dass es sich vielleicht um den ersten Beginn oder um das Abklingen einer diffusen Glomerulonephritis handelt," and admits, "gelingt es mittelst dieses Momentes *vielleicht* [his underscore] eine anatomische Abgrenzung der herdformigen gegen die abklingende Glomerulonephritis vorzunehmen." In a later discussion[65] theoretical assumptions as to the origin of the two "diseases" are introduced for, "die herdförmige Glomerulonephritis . . . ist manchmal toxisch, meist wohl bakteriell bedingt und stellt so einen in

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nephritis had no separate existence but was only the latent stage of hemorrhagic Bright's disease as seen in patients who had forgotten or never recognized the symptoms of the first stage of the disease. This conclusion was fortified by the observation that the course and outcome was the same in the "focal" as in the diffuse glomerular nephritis, for in time the focal cases also either healed or passed into the terminal stage and died of uremia. T. A.

verschiedenen Formen auftretenden übergang zwischen der diffusen Glomerulonephritis einerseits, der embolischen Herdnephritis Löhleins . . . andrerseits dar" (p. 43). And finally, "Die Abgrenzung von der diffusen Glomerulonephritis ist leicht; neben der Herdförmigkeit unterscheidet sich der Prozess von der diffusen Glomerulonephritis dadurch, dass es sich nicht toxisch, sondern bakteriell bedingt ist," and adds "schwieriger erscheint die Abgrenzung gegen die embolische Nephritis"[43] (p. 352). Yet an example of such a case is given, in which this statement appears, "An den Glomeruli lassen sich Bakterien niergends mit Sicherkeit nachweisen." And finally there are cases where the confusion of lesions is so complex that they must be placed in a group of "mixed forms."

All this seems as Löhlein has expressed it somewhat "verwirrend" and rather than add confusion by any attempts at clarification we shall confine ourselves to a statement of our findings and to what seems to us a simple interpretation of them. In the first place, we found no cases in our series that we think need any such special grouping as the "focal glomerulonephritis" which is suggested by Volhard and Fahr. In some of the less violent examples of active hemorrhagic Bright's disease and particularly in the latent stage it is true that lesions in the glomeruli may not be exactly equal in degree and with some subjective interpretation these might possibly be considered instances of focal variation of the disease. Such, however, would be an artificial refinement which is not only unneeded for a simple conception of the relation of the processes involved, but also as Fahr has stated in the first of the quotations we have given would be difficult by anatomical means. There is a time in the development of hemorrhagic Bright's disease when the lesions of destructive fibrosis and metallaxis have developed that a patchy and a diffuse involvement of the kidney can be differentiated and as we have previously stated the variation in this factor is of considerable importance in the ultimate course of development of the disease. We trust that there will be no confusion of our use of the terms patchy and diffuse metallaxis with what has been described above as "focal and diffuse glomerulonephritis." Our terms are merely descriptive of the fate of the kidney parenchyma in hemorrhagic Bright's disease as the disease progresses and do not refer, as do Volhard and Fahr's terms, to different types of renal disease.

In the case of focal embolic nephritis associated with bacterial endocarditis this series has shown no examples, at least in its uncomplicated form. In two instances (Cases VIII and XIII) examples of active hemorrhagic Bright's disease associated with bacterial endocarditis (diffuse glomerulonephritis), among the majority of the glomeruli which showed typical intracapillary or extracapillary glomerulitis, an occasional embolic lesion could be found (Fig. 18 and Plate XIII A). These could be considered the "mixed forms" of Volhard and Fahr. Two other cases of bacterial endocarditis presented typical hemorrhagic Bright's disease and in another there was a septic diffuse inflammation of the kidney with embolic abscesses.

It seems to us that this material illustrates very completely what renal lesions may complicate a bacterial endocarditis. In this affection a source of minute bacteria-containing emboli is present, so that an embolic form of kidney damage may occur. This by chance was not found in our series, but as we have stated has been clearly established. The septic infection in the heart is flooding the circulation with toxic products so that the lesions of a hemorrhagic Bright's disease which are its typical result may be expected. Or both embolic and toxic factors may affect the kidney with the production of both their typical results. And finally the kidney may suffer from a purulent infiltration by septic inflammatory processes with abscess formation. Again we see a series of reactions in the kidney to a unified etiology that present no essential differences but those of degree or intensity. Why then split them into groups of classification which are even more complex than are the facts themselves?

Our observations as a pathologist have therefore brought us to a similar point of view to that reached by the Clinician. The latter by studying the changes in the urinary sediment was able to choose by quantitative methods significant characteristics from among qualitatively similar processes, and so establish a classification. His quantitative methods being more exact allow a more rigid determination of his types, but with the same principle of quantitative determination the morphologist can also establish subdivisions of the disease that correspond surprisingly well in actual application with those of the Clinician. Just as to the latter the urine of all individuals shows the essential lesions of Bright's disease, that is casts and albumin, and the diagnosis of disease depends only on the increase of these abnormalities over an arbitrary normal limit, so the pathologist never sees a kidney "normal" in its structure. He has unfortunately no strictly quantitative methods at his disposal, but with reasonable exactness he can sort his specimens into groups by means of a procedure that is essentially similar. The definition of the Clinician for Bright's disease may therefore be supplemented by the Pathologist. Bright's disease is that condition in which more protein and a greater number of casts are to be found in the urine than during health, these abnormalities being the result of a combination of varying degrees of degenerative, inflammatory, and arterial sclerosing processes in the kidney, greater in extent than found in the average normal individual.

It may be objected that the Pathologist in the adoption of the present scheme and classification has overlooked possibilities at his disposal. Since by detailed examination he might be able to recognize finer differences in the lesions of the kidney than he has made use of in this classification, it may be claimed that he should establish groups that would recognize their existence. The argument depends probably on the personal attitude of the classifier. Are we to establish as many different groups as our morphological acuity allows us to distinguish, or are we to reduce the individual cases to as few inclusive subdivisions as our findings and reason allow? Either method may be pushed to the absurd; a middle way must be found and our personal inclination leads us toward the method by similarities and simplification rather than to dissimilarities and complexity. The only check upon this way that we have taken is the danger of ignoring in our attempts at unity some significant difference in the etiology or histiogenesis of the disease, and the final and only criterion of the validity of our attempt will be its usefulness for both the study and treatment of the disease.

As we have said, Bright's disease is the response of the kidney to alterations in its environment, especially to the irritation of toxic substances From this comes the unity of the disease. The kidney, being an organ composed of many tissues, responds in diverse ways depending on the ability of reaction of these individual tissues. From this comes the disease's complexity. Differences in the "nature" of the poisonous substance, that is the etiological factor, doubtless also play their part in certain specific cases at least in the production of the organ's varied response, but this would seem to be perhaps a secondary factor, as increasing evidence indicates the predominating importance of bacterial infection in the production not only of chronic renal disease but also of the vascular lesions, both local and general, which are so commonly associated with it.

This last would seem a logical concluding paragraph for the Pathologist. However, he sees in it an expression of completion and finality that is far from an accurate representation of his mental state in the matter, and if the addition that he now makes leaves his presentation in the air, as it were, the dissatisfaction that he feels with it will at least be accurately mirrored. But first he would protest that this feeling, that is doubtless shared by all his confreres in Pathology, is neither one of "cynical aquiescence" to a philosophy of despair nor a "confession of frustration" (p. 3). That such might have been the readers interpretation of his attitude from the reading of some of his discussions of the morphological aspect of the problems of the disease, it must be admitted. His pessimistic attitude toward the possibility of any great advance of our knowledge of this disease by the morphological method may well be the result of his own inability to add new lesions and processes as a personal contribution to the multitude of descriptions that have already been given, but it certainly does not come from any disrespect for the science of morphology in whose tradition he was trained.

It is in the experimental method, however, that he prefers to seek an elucidation of the problems which morphology has raised. The correlation of function and anatomical structure which has not been touched on in this discussion at all, and which is the basic and all important part of the problem, is still a complete mystery. It is by experimentation, under controlled and simplified conditions, that this ultimate phase must be attacked. And it is from such endeavor, he believes, that a more satisfactory theory and classification of Bright's disease will eventually evolve.

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PLATES LXXIII TO XCVIII

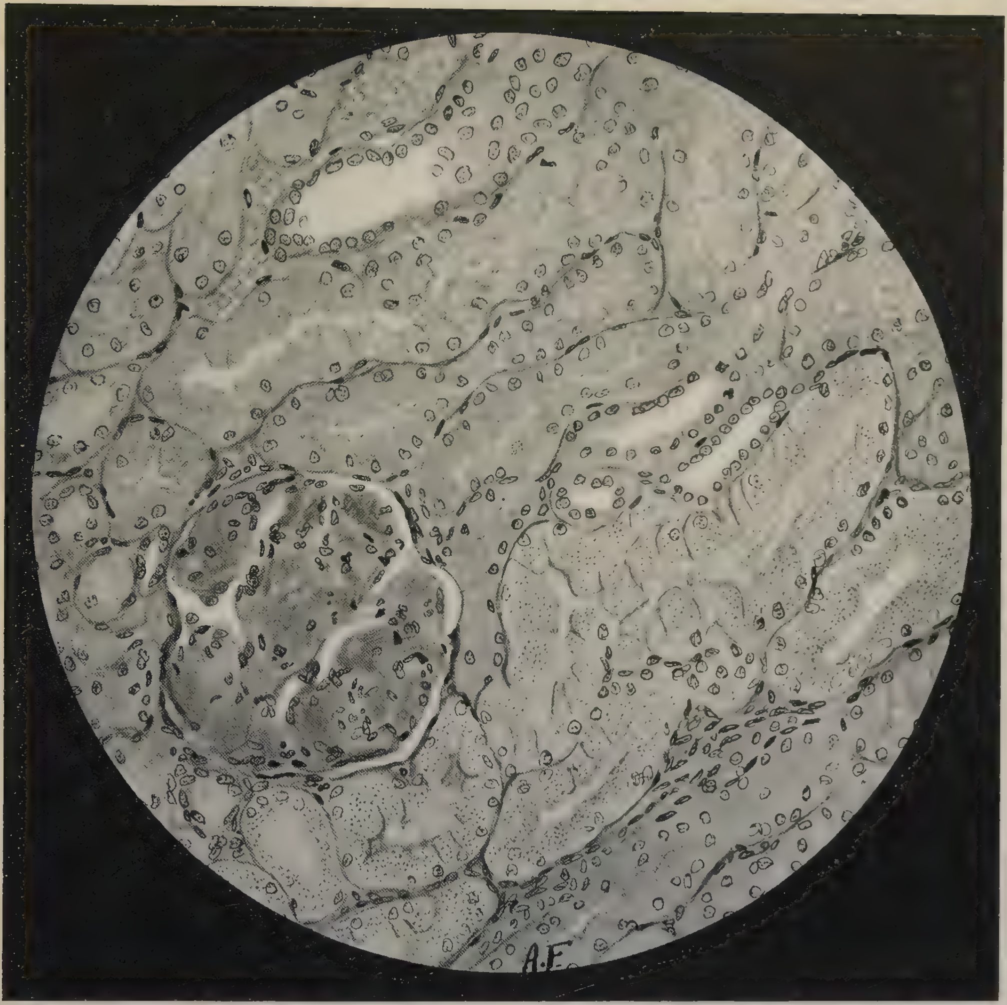

Plate LXXIII

Case lii. Degenerative Bright's disease, early stage of pyogenic form.

There is a moderate infiltration of the glomerulus with amyloid. All of the tubules show a cloudy swelling of the mild type in their epithelial cells. A group of tubule cross sections where the epithelium is greatly swollen and coarsely granular is also seen. There are no evidences of any inflammatory process in the interstitial tissue. (Cf. Plates lii a and b.)

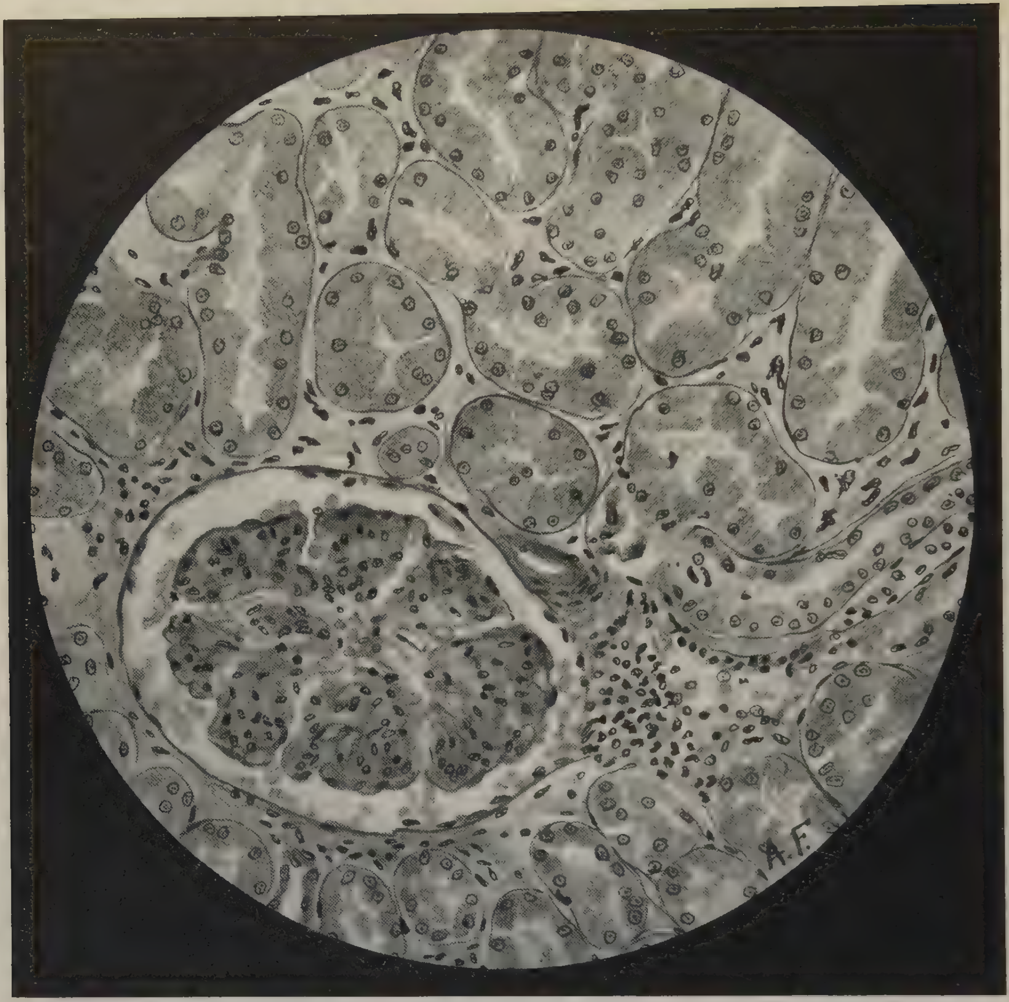

Plate LXXIV

Case lviii. Degenerative Bright's disease, non-bacterial form.

There is a marked cloudy swelling of the epithelium of the convoluted tubules. The glomerulus is essentially normal except for some detritus and desquamated cells in Bowman's space. Around the afferent arteriole (to the right of the glomerulus) is a collection of inflammatory leucocytic infiltration, in which are quite a few polymorphonuclears. Such areas of inflammation are scattered throughout the cortex. (Cf. Plates lviii a and b.)

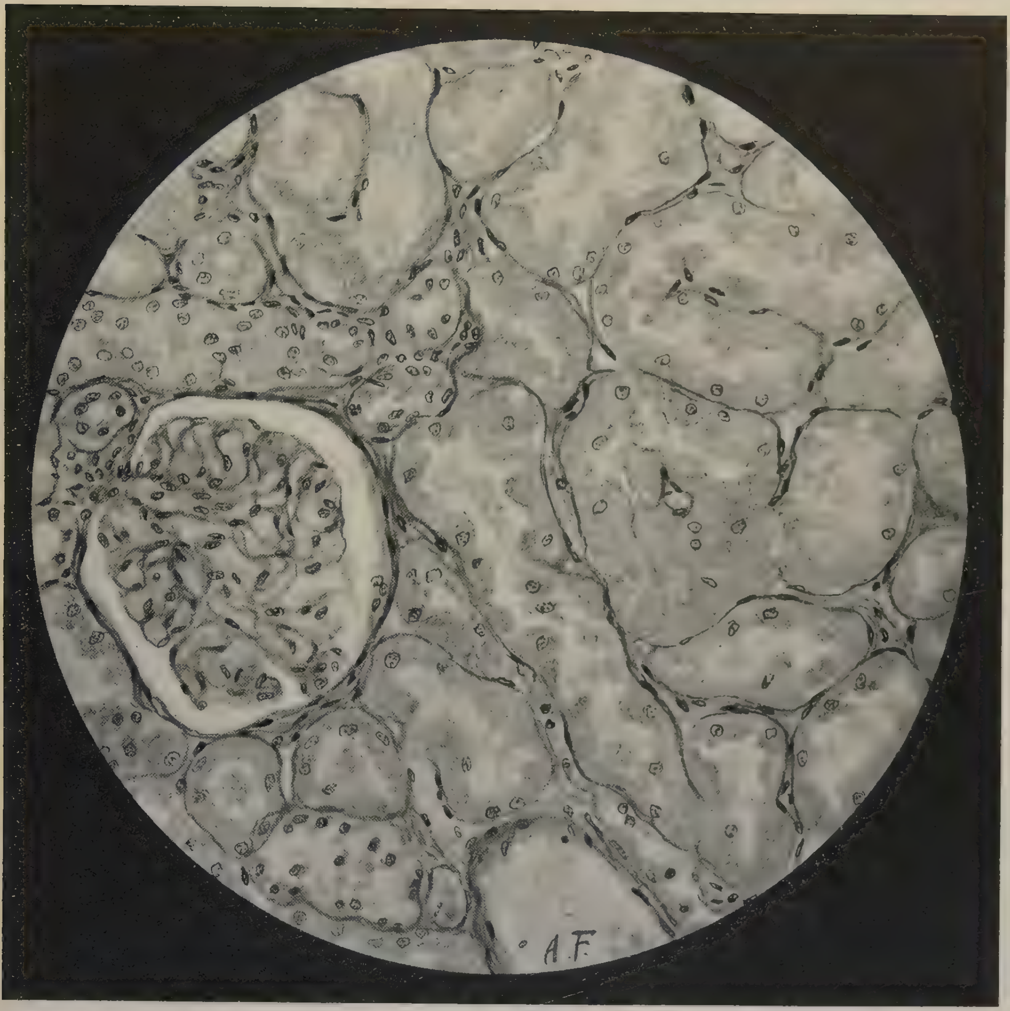

PLATE LXXV

Case XLVIII. Degenerative Bright's disease, early cryptic form.

Except for the marked swelling and granular protoplasm of the epithelial cells of the tubules no pathological processes can be seen. (Cf. Plates XLVIII A and B.)

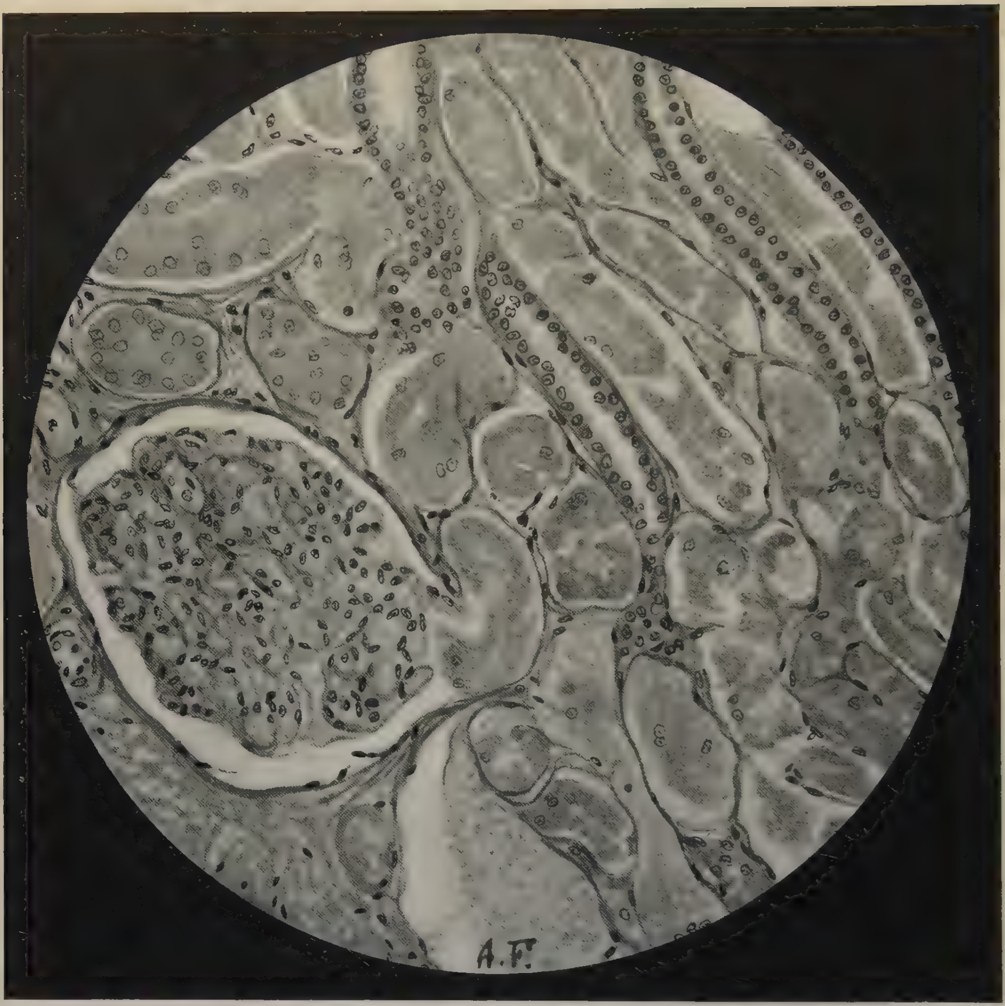

Plate LXXVI

Case xlix. Degenerative Bright's disease, cryptic form.

The glomerulus is normal. The epithelium in most of the sections of the convoluted tubule is necrotic, only an occasional nucleus remaining. Note the necrotic mass filling the neck of the proximal convoluted tubule at its origin from Bowman's space. The interstitial tissue is normal, as are sections through the connecting tubules, whose low dark staining epithelium is well preserved. (Cf. Plates xlix a and b.)

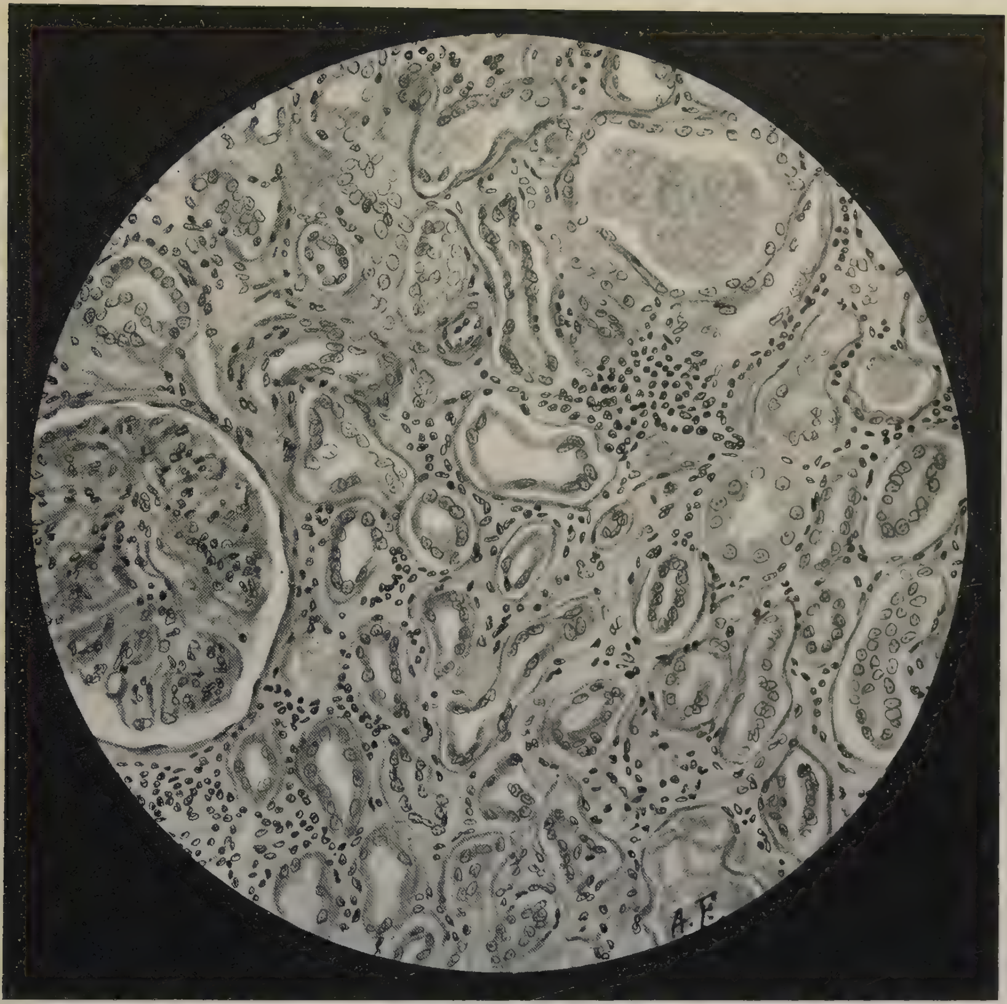

Plate LXXVII

Case L. Degenerative Bright's disease, late cryptic form.

The glomerulus is normal. There is a diffuse moderate increase in the amount of interstitial connective tissue with areas of leucocytic infiltration. Among the leucocytes, which are chiefly "round cells," are a few polymorphonuclears. The tubules are irregular in size and shape and are lined with a regenerated epithelium of atypical form, as is evidenced by the excessive number of the nuclei and their irregular distribution. (Cf. Plates L, A and B.)

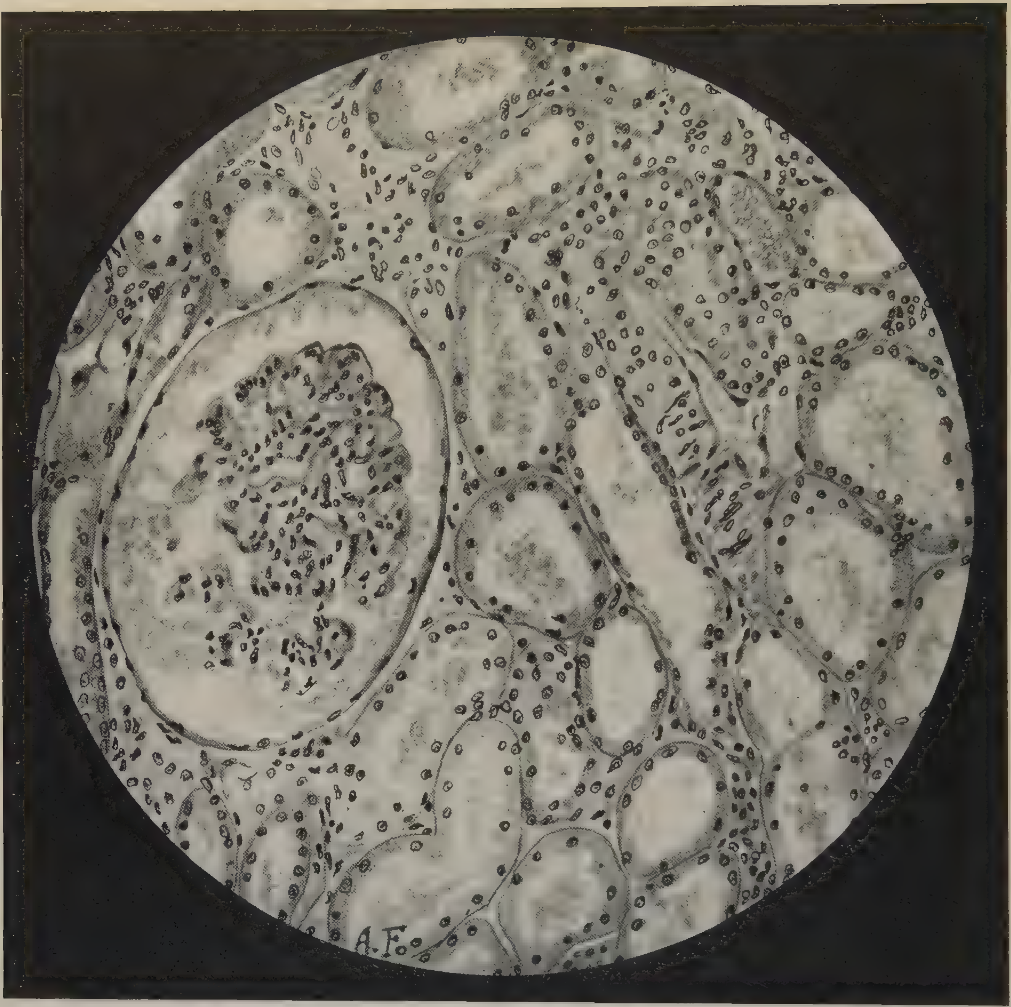

PLATE LXXVIII

Case LIX. Degenerative Bright's disease, non-bacterial form.

The tissues of the glomerulus appear normal but the damage to its structure is evident from the large amount of granular material which has leaked into Bowman's space. The epithelial cells of the convoluted tubules are markedly granular and the lumen of the tubule is filled with debris. There is a slight leucocytic infiltration of the interstitial tissue. (Cf. Plates LIX A and B.)

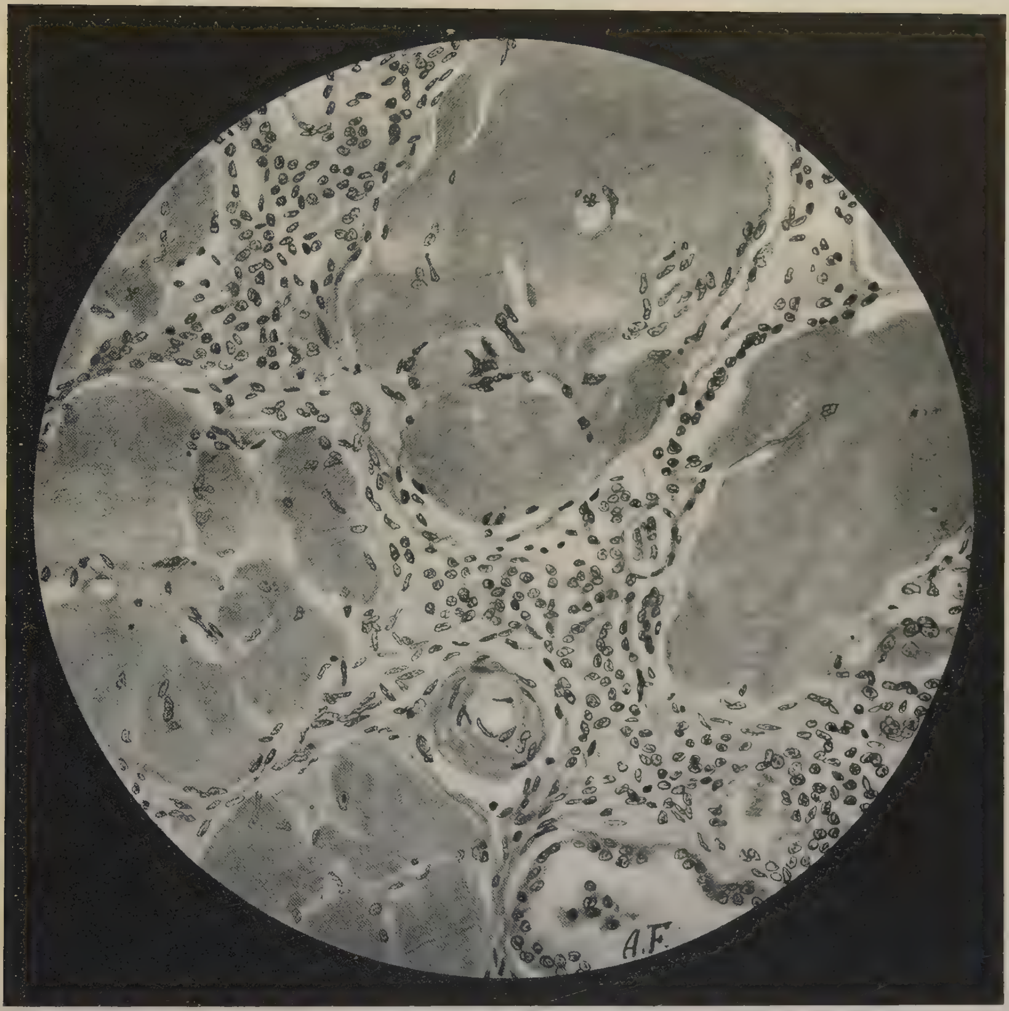

PLATE LXXIX

Case LV. Degenerative Bright's disease, late stage of pyogenic form.

The glomeruli are heavily infiltrated with large masses of amyloid, their tissues being almost completely replaced by the infiltration. A small arteriole is also seen in the lower middle third of the picture whose wall is thickened with the infiltration. There is also present a marked inflammatory infiltration of the interstitial tissue with leucocytes. Most of these are "round cells" but a few polymorphonuclears can be found. The tubules are mostly collapsed, many existing only as clumps of atrophied cells. (Cf. Plates LV A and B.)

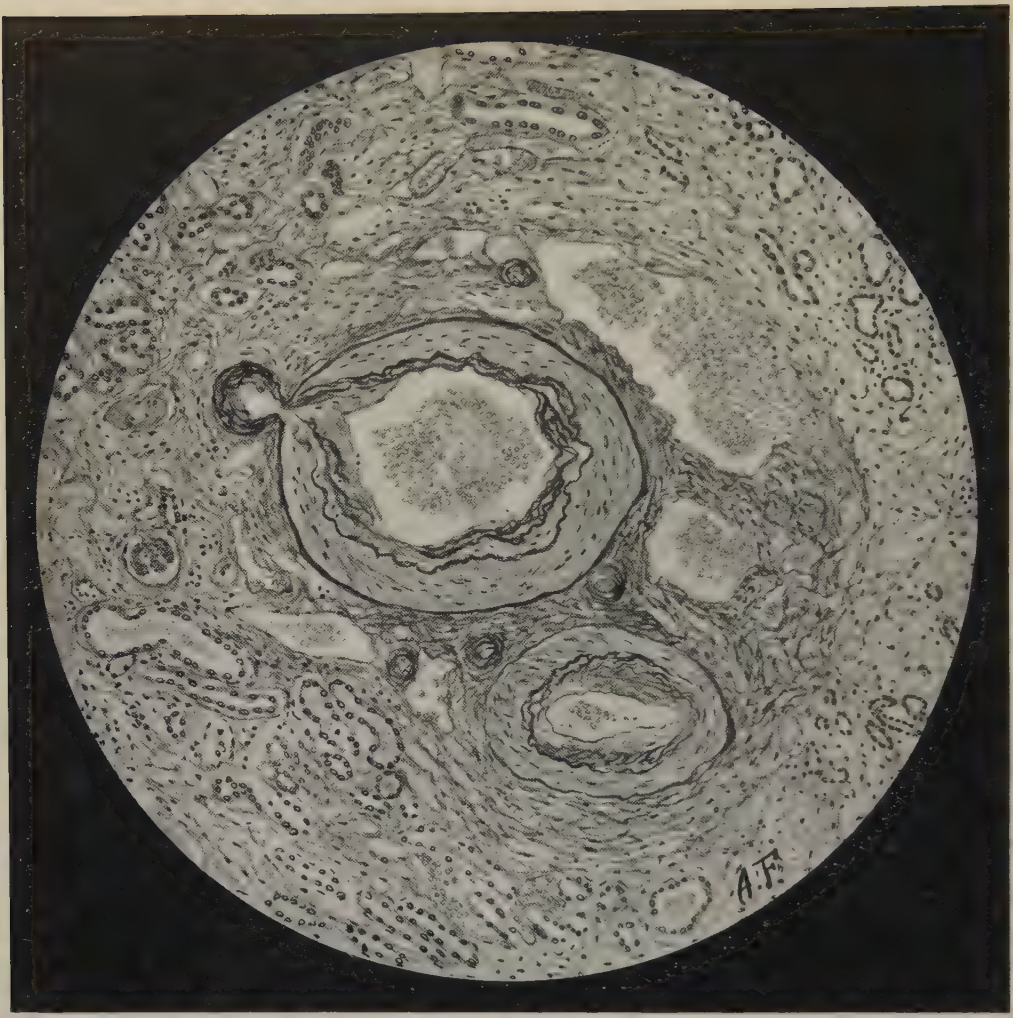

PLATE LXXX

Case LXV. Arteriosclerotic Bright's disease.

The low power field shows the typical sclerotic lesions in the moderate sized arteries lying at the junction of cortex and medulla. The proliferation of the elastic tissue in the vessels is well shown. Near them are several dilated veins filled with red blood cells. Throughout the rest of the section there is a diffuse proliferation of the connective tissue with consequent atrophy, or in places dilatation, of the tubules. (Cf. Plates LXV A and B.)

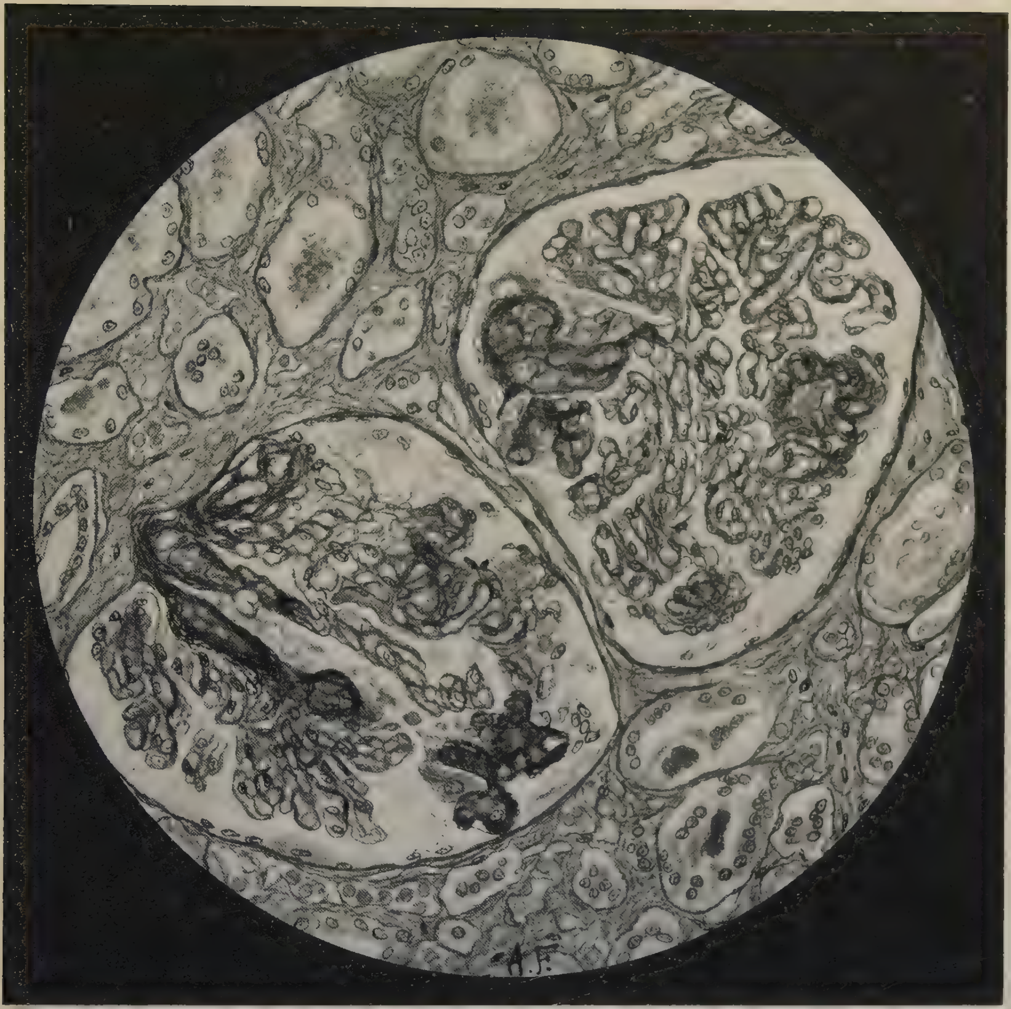

Plate LXXXI

Case LXV. Arteriosclerotic Bright's disease.

The section does not pass through the afferent arteriole exterior to the tuft. Throughout both tufts, however, the extension of the fibrosing process along and around the capillaries of the tuft is well seen. This thickening of the capillary walls is just evident in some places while in others the capillaries have been obliterated by it. There is the usual fibrous proliferation of the interstitial tissue throughout the section with distortion of the tubules and atrophy of their cells. (Cf. Plates LXV A and B.)

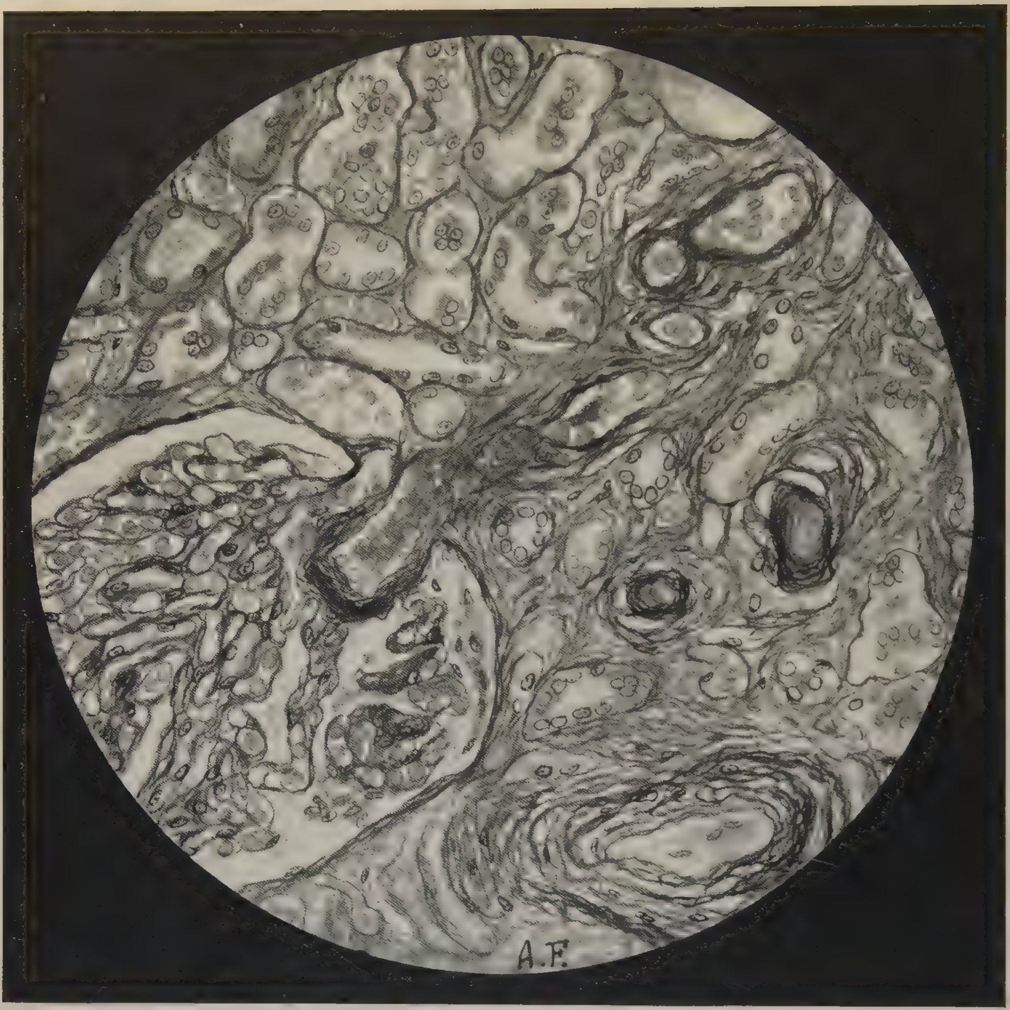

Plate LXXXII

Case LXV. Arteriosclerotic Bright's disease.

In the lower part of the figure is a small artery whose wall is greatly thickened and fibrous. Above this are seen sections through the tortuous terminal portion of the afferent arteriole just as it enters the glomerular tuft. Its wall is also greatly thickened by a fibrillar proliferation. The tuft of the glomerulus is, however, still uninvolved. Throughout the section, particularly in its left lower half, the interstitial tissue is increased and fibrous and there is a marked deformity of the enclosed tubules. (Cf. Plates LXV A and B.)

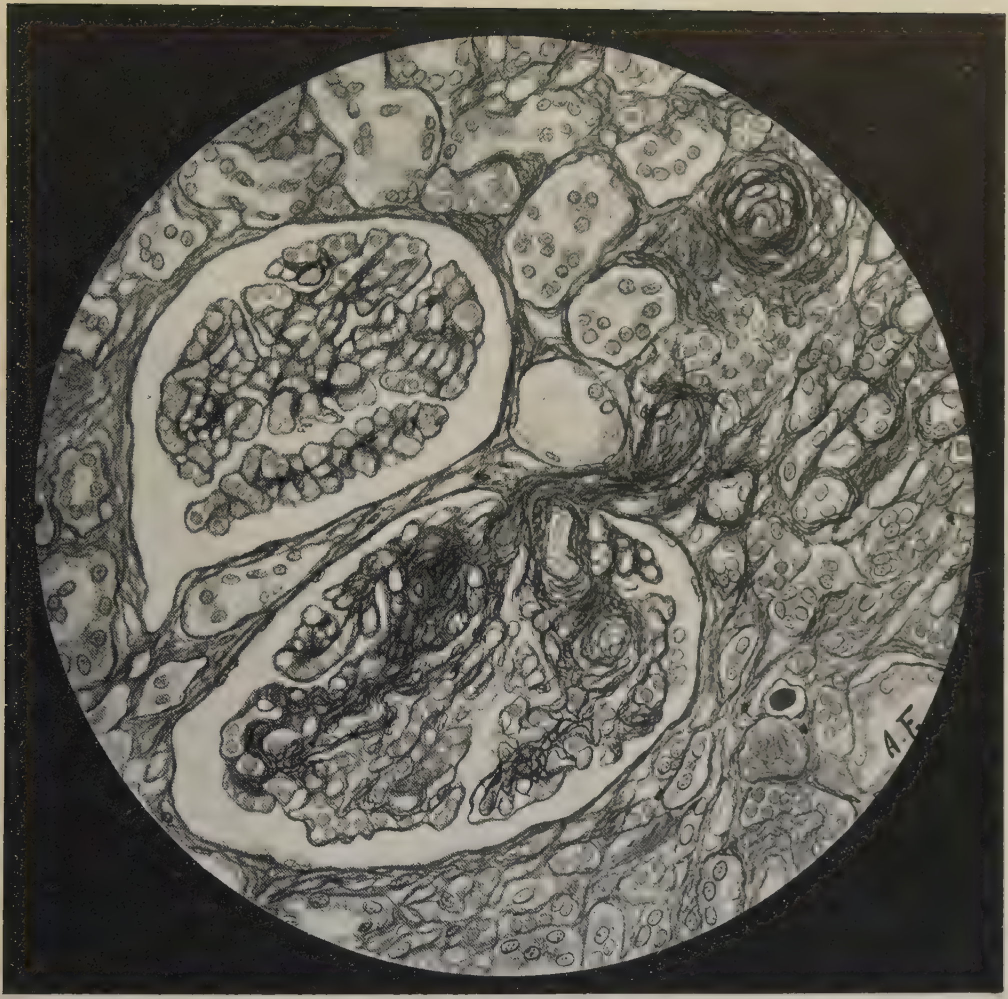

Plate LXXXIII

Case lxv. Arteriosclerotic Bright's disease.

In the upper tuft there is a just perceptible thickening of the capillary walls. The thickened afferent arteriole to the lower glomerulus may be followed into the tuft where the fibrous thickening extends out along the capillaries. A considerable portion of the structure is thus destroyed. The usual connective tissue proliferation of the interstitial tissue and tubular atrophy is present. (Cf. Plates lxv a and b.)

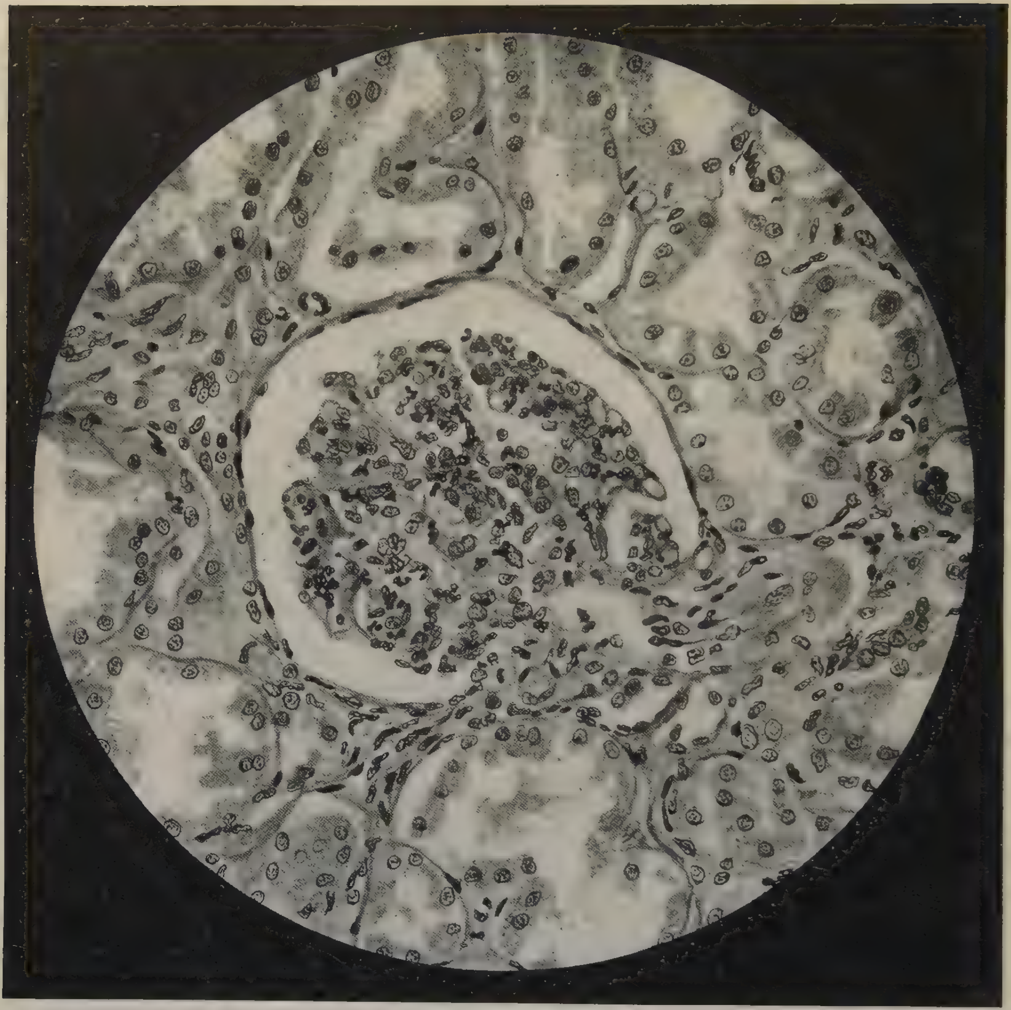

Plate LXXXIV

Case lxviii. Arteriosclerotic Bright's disease.

A glomerulus has been selected which shows the inflammatory lesions commonly encountered in this form of the disease. The afferent arteriole is thickened. There is no definite fibrosis of the tuft but scattered throughout it are many inflammatory leucocytes, some of which are polymorphonuclears. There are marked degenerative changes in the epithelium of the tubules. The interstitial tissue in this field is essentially normal. (Cf. Plates lxviii a and b.)

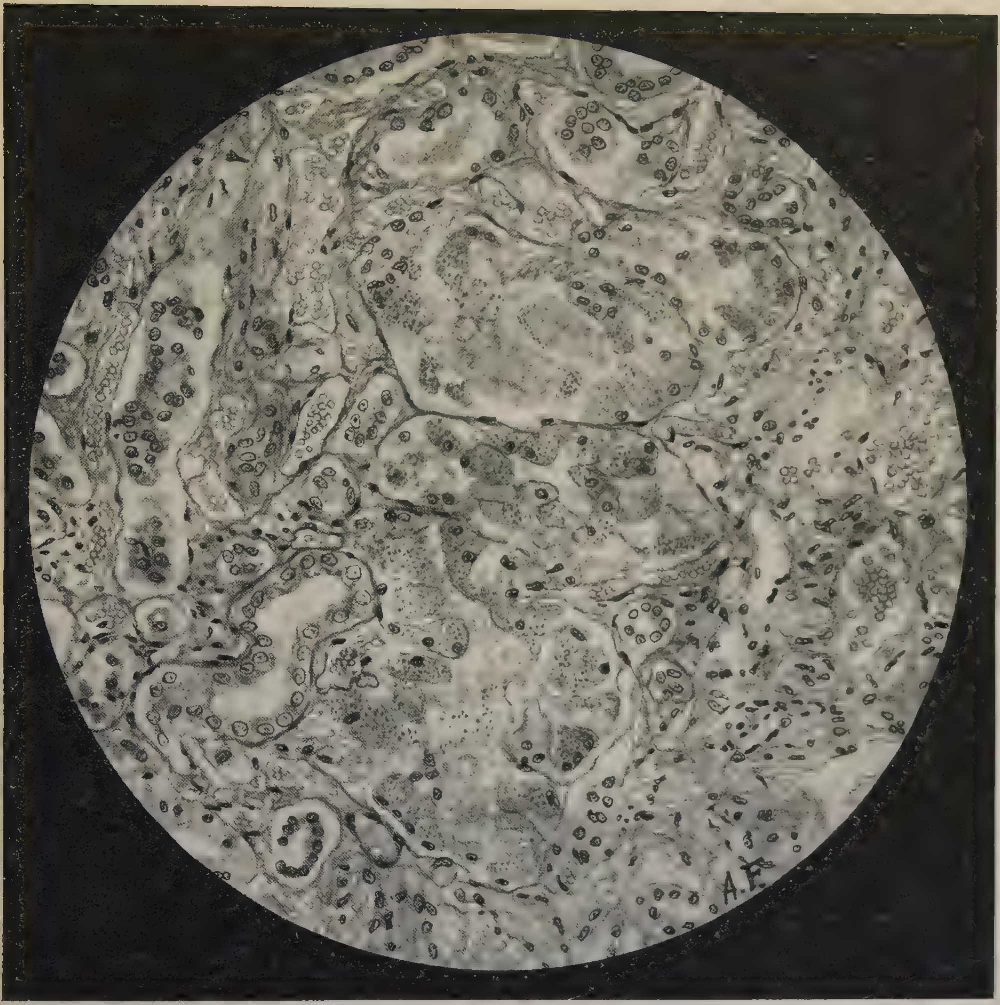

Plate LXXXV

Case lxv. Arteriosclerotic Bright's disease.

The section shows the marked degenerative changes in the tubular epithelium which may complicate this form of Bright's disease. The tubules throughout the section are greatly distorted by the proliferation of connective tissue between them. In this connective tissue are a moderate number of leucocytes. Around the periphery of the field the tubules are collapsed and their epithelium atrophied. In the center of the field are some enormous irregular shaped tubules whose epithelium was previously hypertrophied. The epithelial cells are now, however, in various stages of cloudy swelling, necrosis and desquamation. Note the enormously dilated capillaries, crowded with red blood cells, which are scattered throughout the developing connective tissue. (Cf. Plates lxv a and b.)

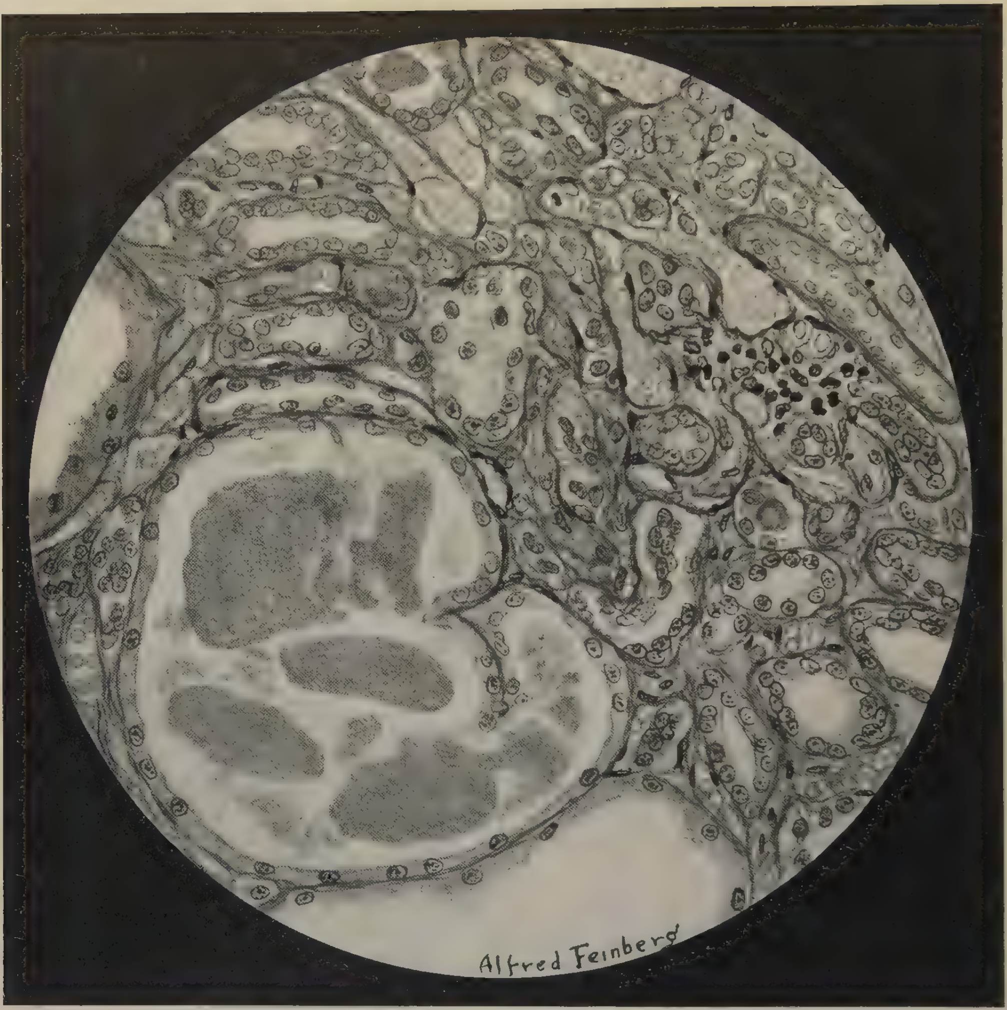

Plate LXXXVI

Case lxvi. Arteriosclerotic Bright's disease.

A greatly dilated tubule is seen with atrophied epithelium whose lumen is filled with coagulated material. Throughout the rest of the section there is a marked fibrous proliferation of the interstitial connective tissue with development of collagen fibrils and an occasional area of leucocytic infiltration. The tubules show marked atrophy and their epithelium is atrophic and atypical. In many the lumen has been obliterated by these changes. (Cf. Plates lxvi a and b.)

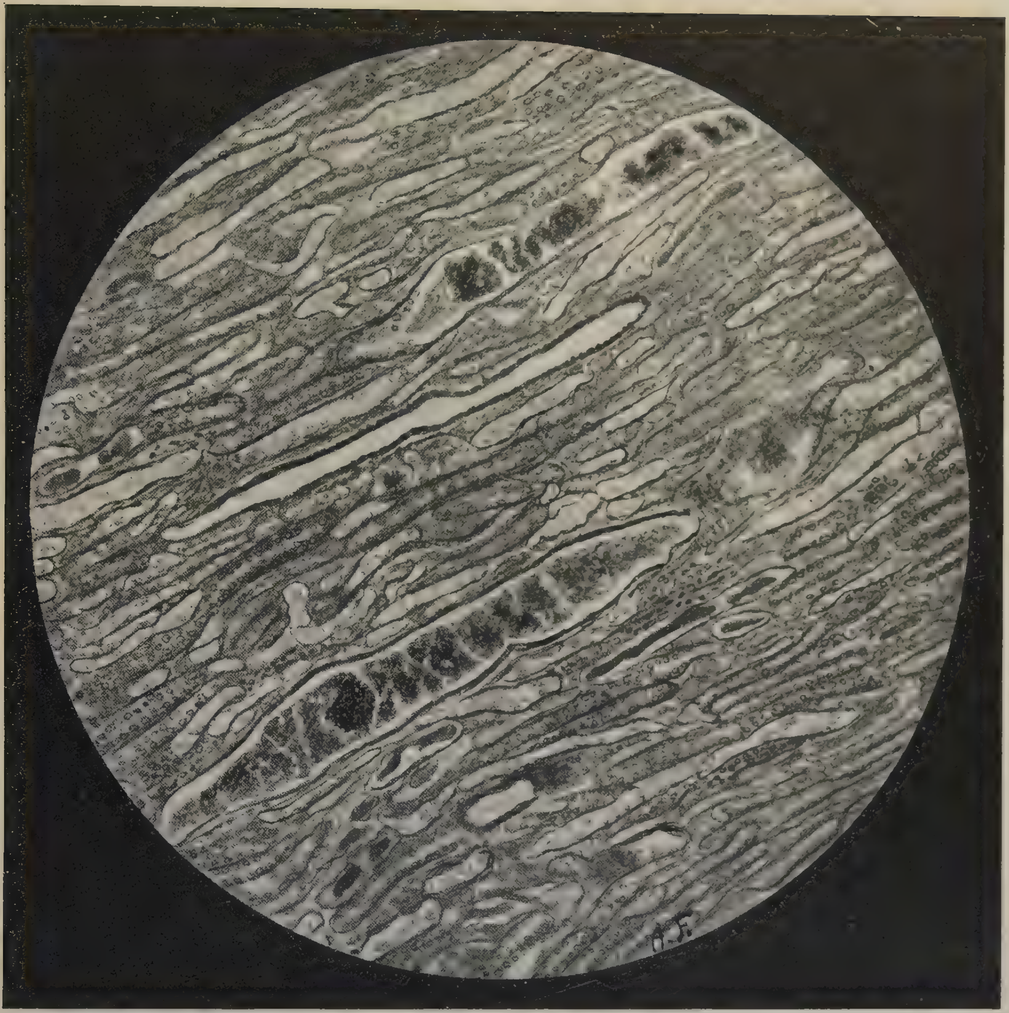

Plate LXXXVII

Case LXVI. Arteriosclerotic Bright's disease.

The section is taken from the medulla and in two ducts of Bellini are seen the large broad renal failure casts. Their tremendous size may be appreciated by comparison with the hyaline casts of usual diameter which lie just below them. Their heterogeneous composition and poorly organized form are clearly evident in the histological preparation. Except for the marked dilatation of the capillaries between the tubules, the tissues of the medulla show no significant lesions. (Cf. Fig. 11, 17, Plates LXVI A and B, XCVIII.)

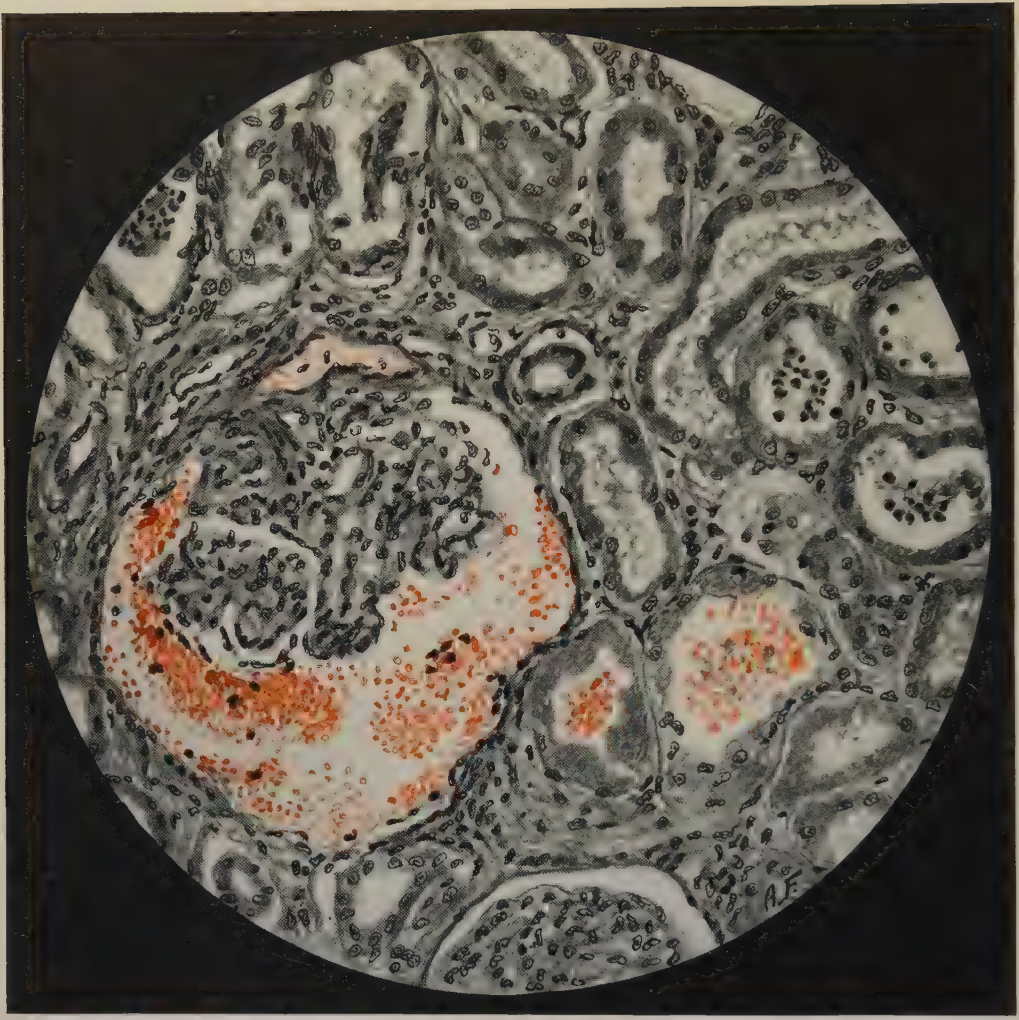

Plate LXXXVIII

Case xiii. Hemorrhagic Bright's disease, active stage.

The glomerular tuft shows a leucocytic infiltration and the capsular space is filled with a large collection of red blood cells. These red cells have escaped into the convoluted tubule and may be seen in the lumens of its sections. Throughout the interstitial tissue there is a definite leucocytic infiltration and polymorphonuclear leucocytes are seen in the lumen of the tubules but proliferative processes are still only of slight degree. The epithelium of the tubules shows various forms of degeneration and in places even necrosis and a considerable amount of resulting debris can be seen in the lumens of the tubules. (Cf. Plates xiii a and b.)

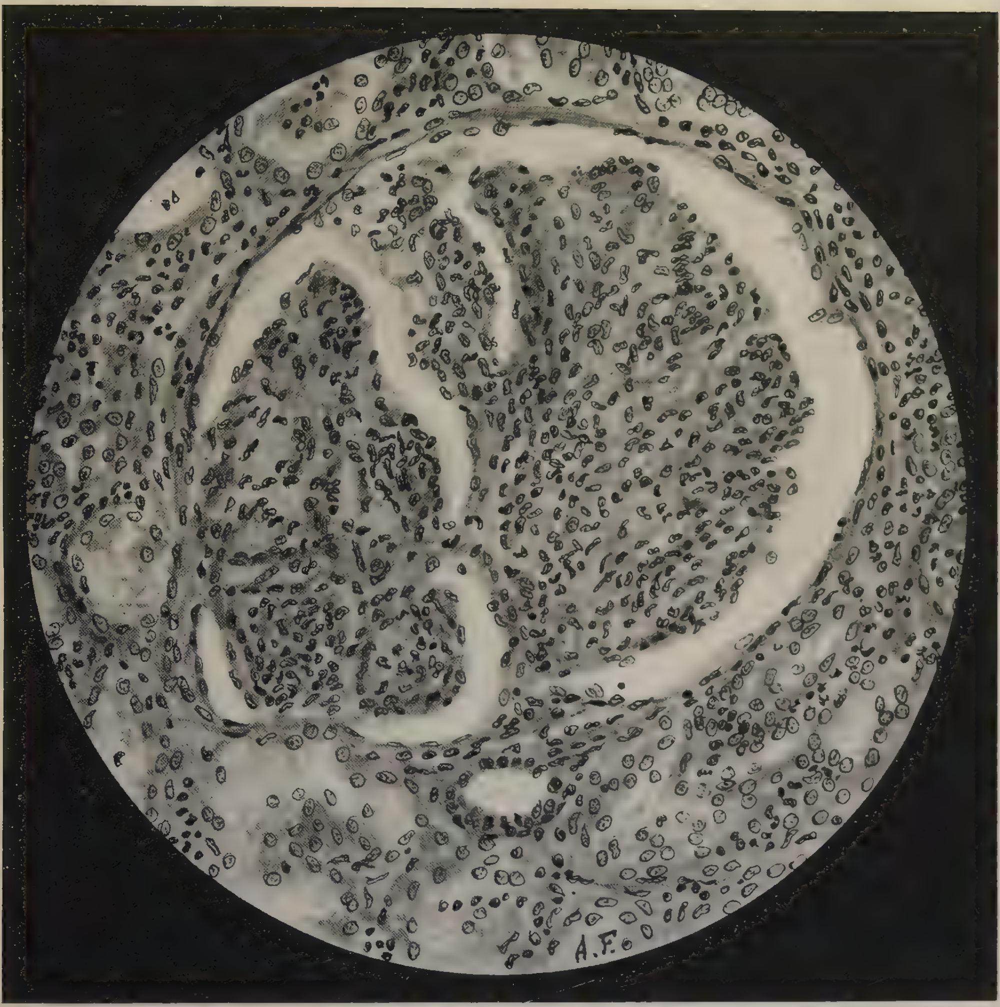

Plate LXXXIX

Case x. Hemorrhagic Bright's disease, active stage.

An enormously enlarged glomerulus occupies the greater part of the section. This enlargement is due to an intracapillary glomerulitis. There is a marked proliferation of the cellular elements of the tuft as well as a severe infiltration of its tissues with leucocytes, many of which are polymorphonuclears. There is only a slight collection of inflammatory products in Bowman's space though adhesions between the tuft and capsule may be seen in several places. Throughout the interstitial tissue there is a diffuse infiltration with inflammatory leucocytes. The epithelium of the tubules shows a granular degeneration and necrosis. At the very upper limit of the section to the right, clusters of atypical regenerative cells may be seen in the tubule lumen. (Cf. Plates x, a and b.)

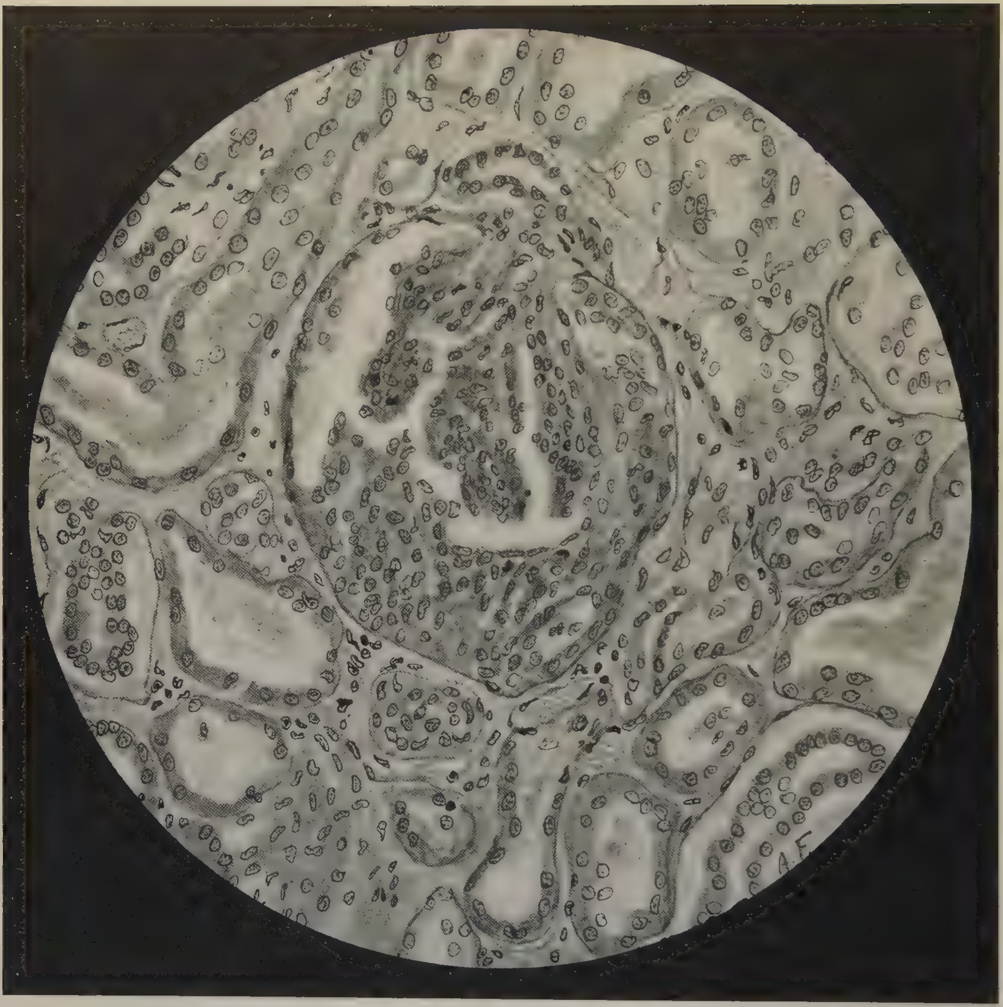

PLATE XC

Case III. Hemorrhagic Bright's disease, active stage.

A glomerulus is seen which shows the typical "crescent" formation of the extracapillary form of glomerulitis. The tuft is compressed and Bowman's space is almost completely filled with a mass of inflammatory cells. At this early stage the tissue is still cellular and shows little development of collagen fibrils. The damage to the epithelium of the tubules is apparent not only from the debris which fills their lumen but also from the atypical character of the newly regenerated cells which line them. There is only a slight infiltration of the interstitial tissue with leucocytes but there is as yet no significant productive inflammatory changes of it. (Cf. Plates III A and B.)

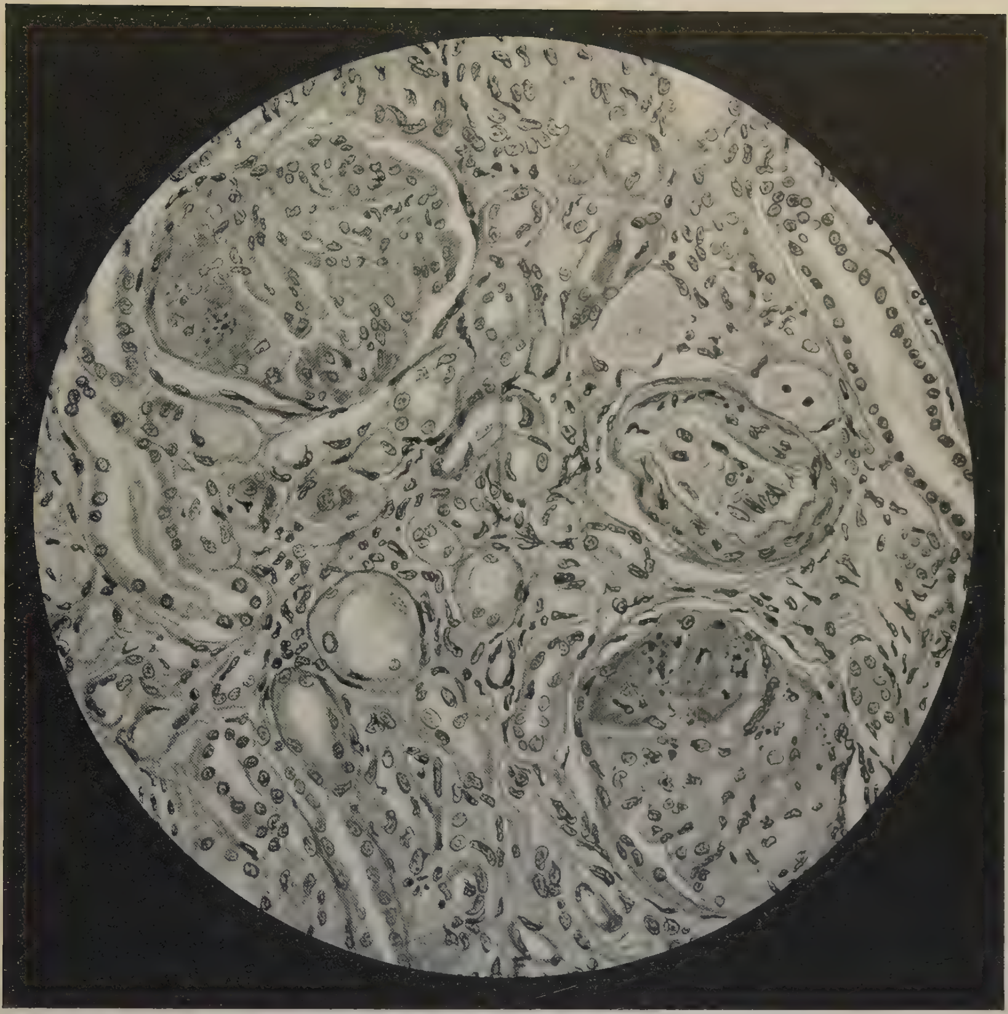

Plate XCI

Case vii. Hemorrhagic Bright's disease, active stage.

Two glomeruli are seen, in both of which are the inflammatory processes of leucocytic infiltration and proliferation of connective tissue. In both there has occurred a hyaline thrombosis of the capillaries of the tuft with resulting areas of necrosis which are filled with nuclear debris. There is a considerable cellular proliferation of the interstitial tissue and a resulting atrophy and distortion of the tubules. Their epithelium is markedly atypical, both the result of atrophy and of atypical regeneration. A small arteriole shows a definite thickening of its wall. (Cf. Plates vii a and b.)

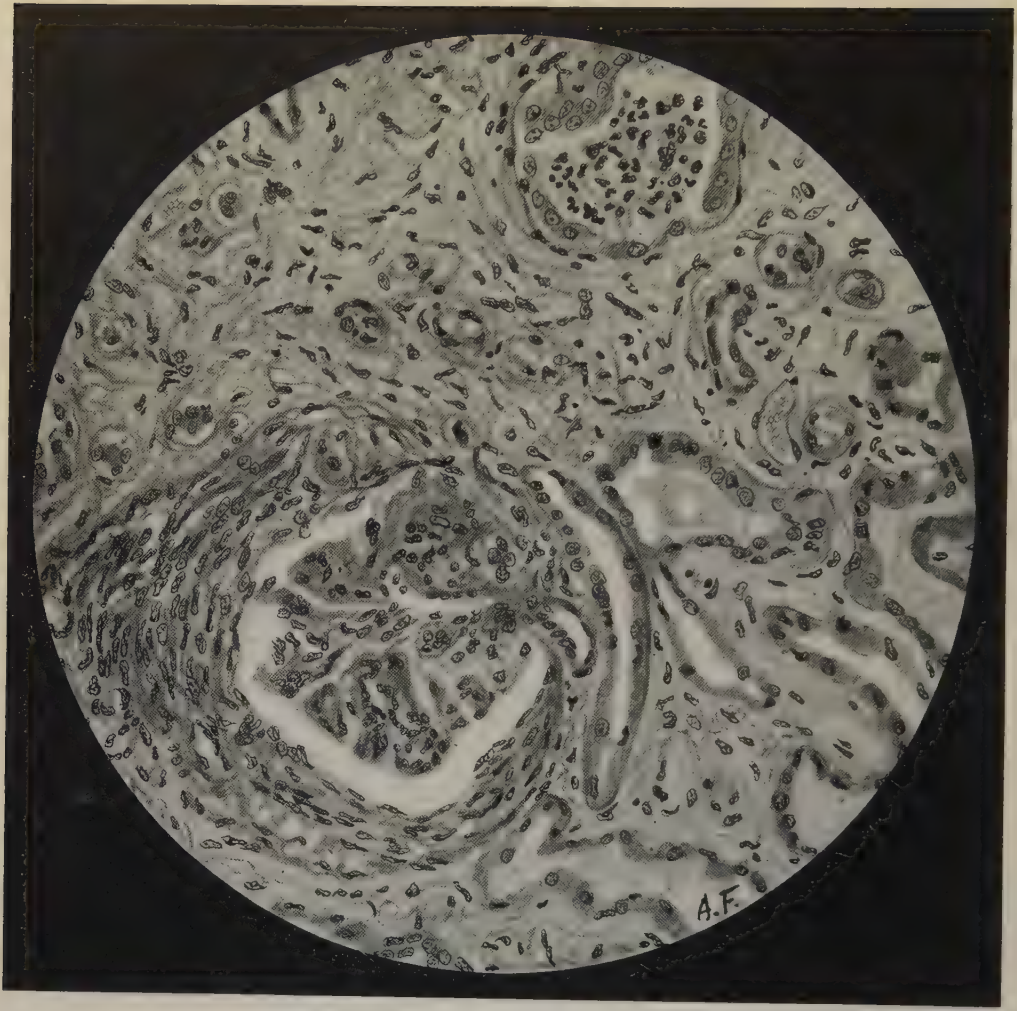

PLATE XCII

Case XXVI. Hemorrhagic Bright's disease, active stage.

A glomerulus is seen in the lower part of the section whose tuft is moderately infiltrated with leucocytes but the most marked inflammatory processes are seen in the capsular space about the tuft. The inflammatory reaction is of the subacute type as proliferative processes both in the tuft and in the capsular space are well marked. Similar proliferative inflammatory processes are seen in the interstitial tissue with consequent deformity of the tubules. The epithelium of these structures is either atrophic or has been replaced by a covering of the atypical regenerative type. The active nature of the inflammatory process is evident from the polymorphonuclear infiltration of all the tissue. There is a collection of these cells in the dilated tubule at the upper portion of the section. (Cf. Plates XXVI A and B.)

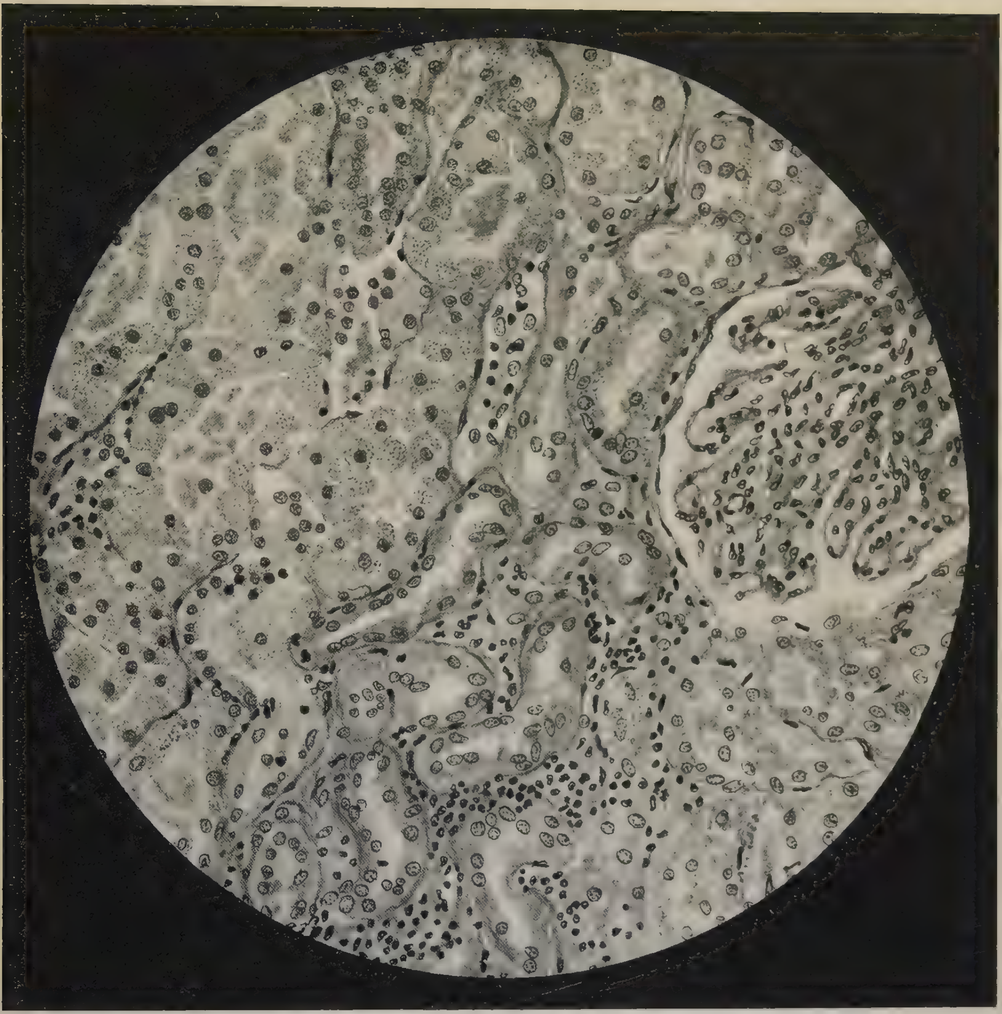

Plate XCIII

Case xx. Hemorrhagic Bright's disease, latent stage.

The glomerular tuft shows no very significant lesions though it is perhaps somewhat more cellular than normal. Throughout the interstitial tissue, which is practically normal in amount, is an irregular infiltration with leucocytes. The tubules in the central portion of the figure are lined with a new covering of atypical regenerative cells. Around the periphery of the figure the epithelium of the tubules shows a very definite cloudy swelling and desquamation. This degeneration and leucocytic infiltration shows that these two processes are actively progressing even in this stage of the disease, which by clinical observation, may be considered a latent one. (Cf. Plates xx a and b.)

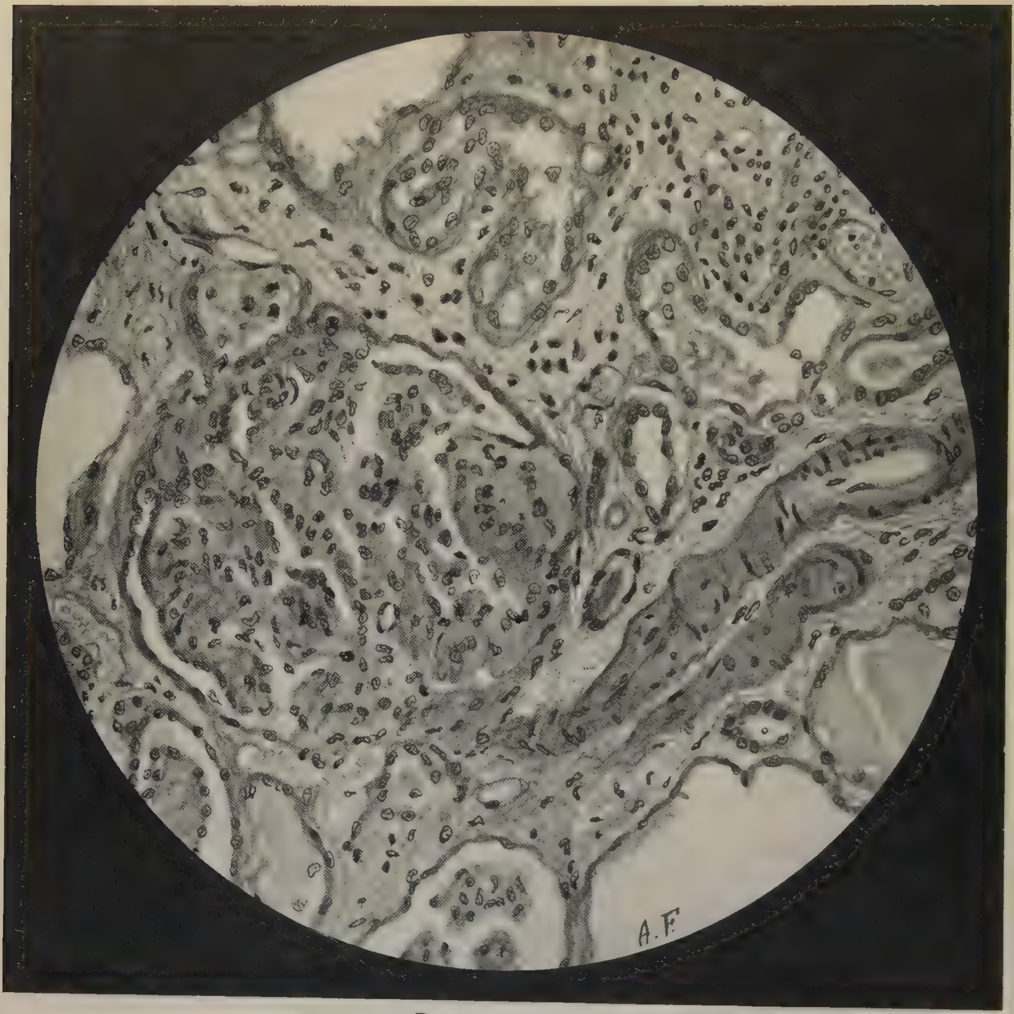

Plate XCIV

Case xxiv. Hemorrhagic Bright's disease, terminal stage.

The glomerular tuft is increased in size and there is a definite proliferation of the tissues of the tuft. Scattered among the proliferating connective tissue cells are many polymorphonuclear leucocytes and the greater part of Bowman's space is obliterated by fibrous adhesions. Both the efferent and afferent arterioles are shown in the section and their walls are thickened. There is a marked increase in the amount of interstitial tissue both as a result of proliferation of collagen fibrils and of infiltration with inflammatory leucocytes. The tubules as a result are distorted and the epithelium is either in different stages of degeneration or has been replaced by an atypical new formed covering. (Cf. Plates xxiv a and b.)

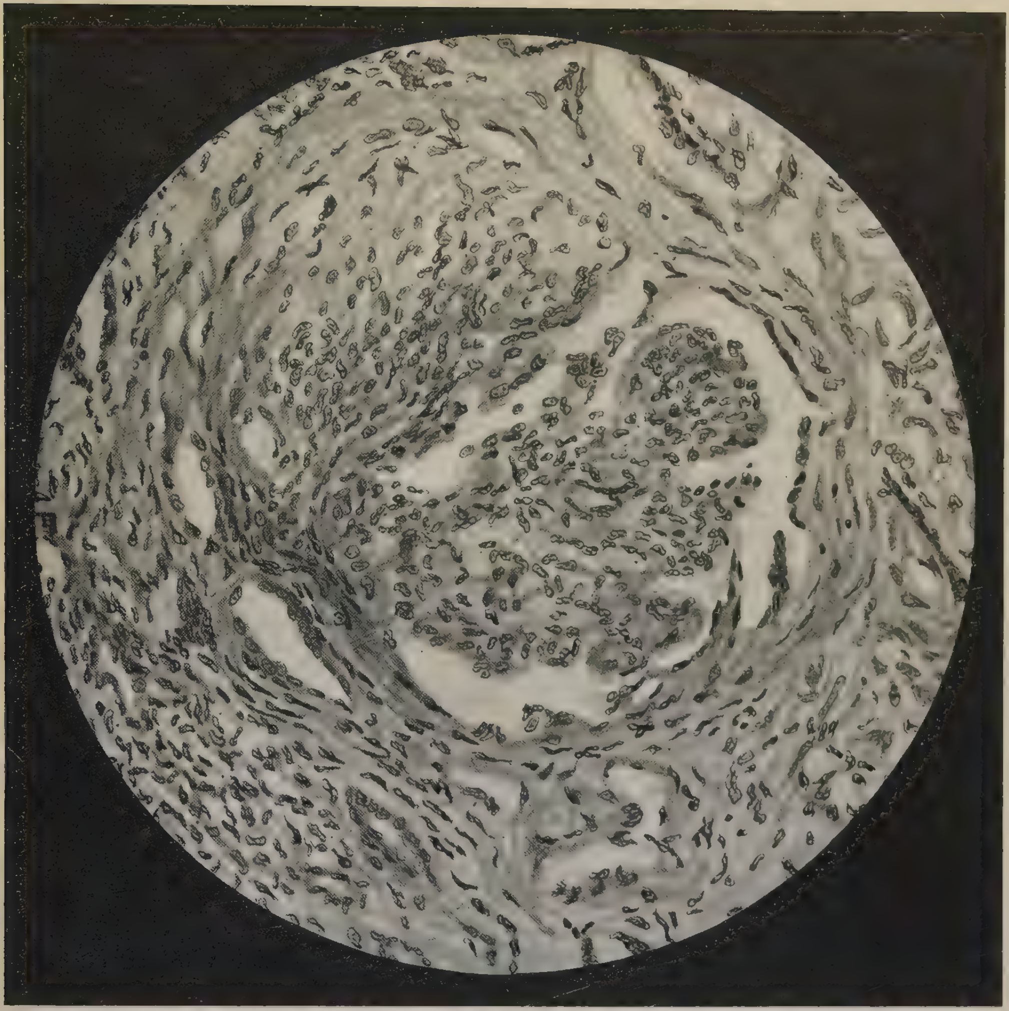

Plate XCV

Case xxix. Hemorrhagic Bright's disease, terminal stage.

A greatly enlarged glomerulus is seen, similar to that shown in Plate lxxxxix except that the processes are in a much later stage. The tuft is infiltrated with leucocytes, but in its lower left hand half there is a diffuse proliferation of fibrous tissue which forms an adhesion and so obliterates Bowman's space. Concentric layers of connective tissue thicken the capsular membrane and throughout the interstitial tissue is seen a heavy cellular proliferation of fibrous tissue. The tubules are greatly compressed and atrophied. (Cf. Plates xxix a and b.)

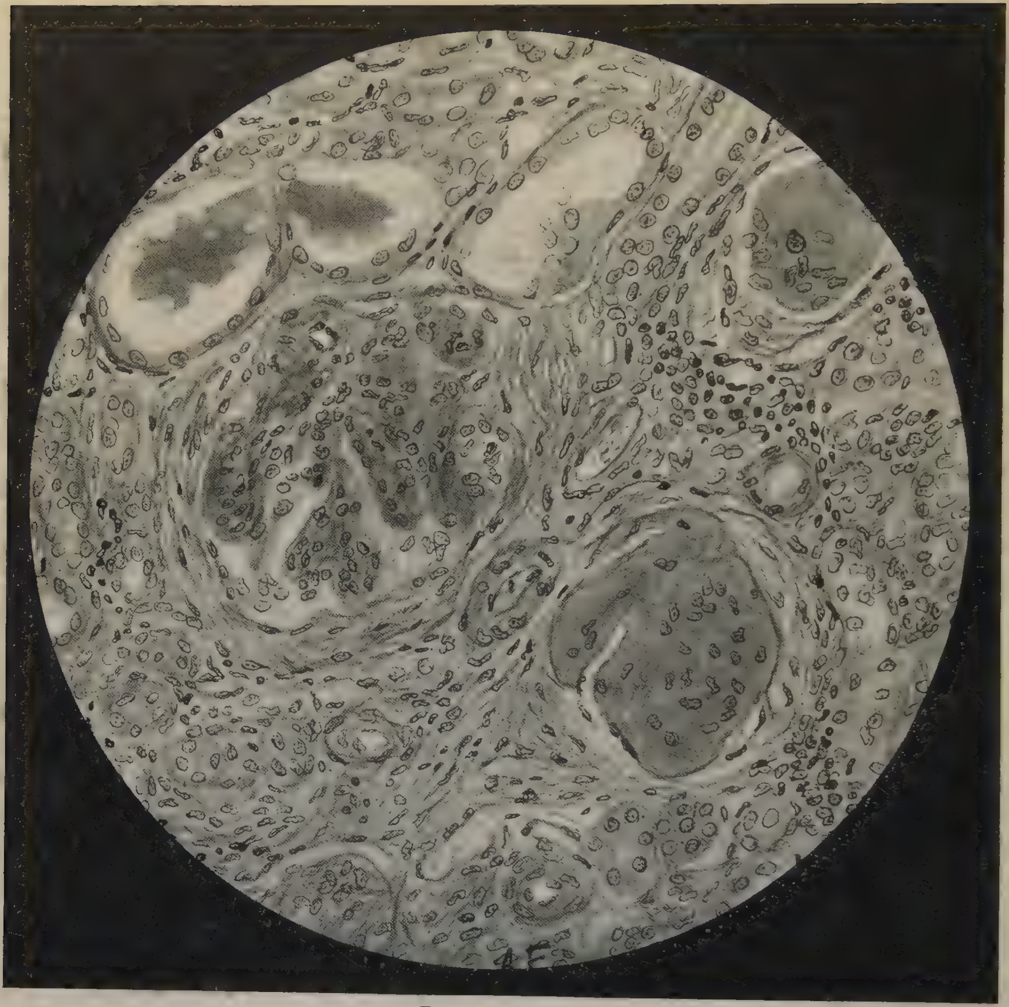

Plate XCVI

Case xliii. Hemorrhagic Bright's disease, terminal stage.

To the left a glomerulus is seen in whose tuft the inflammatory process has produced an extensive proliferation of connective tissue. Its capillaries as a result are collapsed. Bowman's space is occupied by fibrous connective tissue and there are extensive adhesions between the tuft and the capsule. To the right are seen the remains of a glomerulus which has been reduced to a mass of avascular hyaline connective tissue. The interstitial tissue throughout the section shows a marked thickening and infiltration with leucocytes. The tubules are mostly collapsed and their epithelium atrophied. In the upper part of the section some of them are dilated and filled with colloid material. (Cf. Plates xliii a and b.)

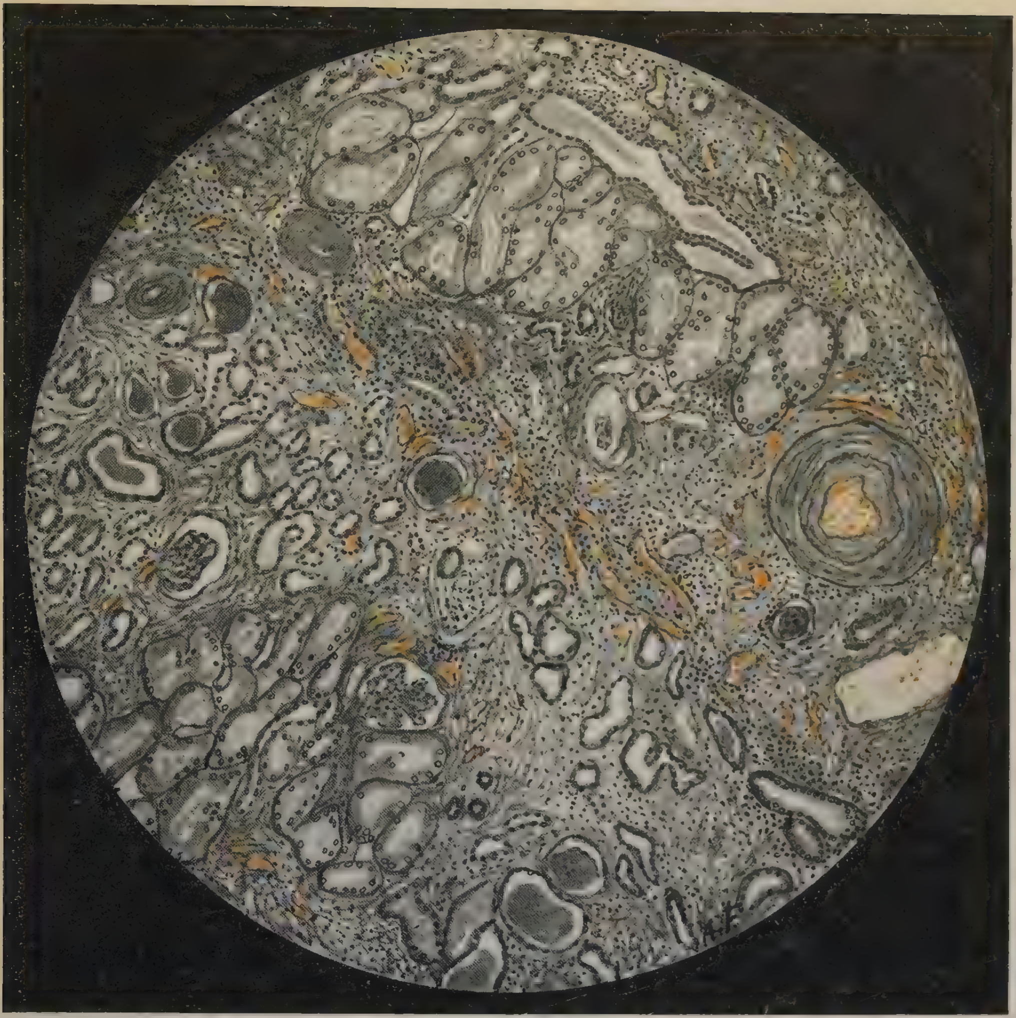

Plate XCVII

Case xliv. Hemorrhagic Bright's disease, terminal stage.

This low power field shows to the right, an artery in the cortex, which is greatly thickened. Throughout the section there is a diffuse irregular proliferation of the interstitial connective tissue, heavily infiltrated with leucocytes, which has caused an atrophy and even destruction of the tubules throughout large regions of the cortex. Two groups of greatly hypertrophied tubules have escaped this destructive process. Their tubules are dilated and filled with colloid material. A few glomeruli still retain their essentially normal structure; others are reduced to clumps of hyaline collagen. Throughout the fibrous areas there is a marked irregular dilatation of the enclosed capillaries. (Cf. Plates xliv a and b.)

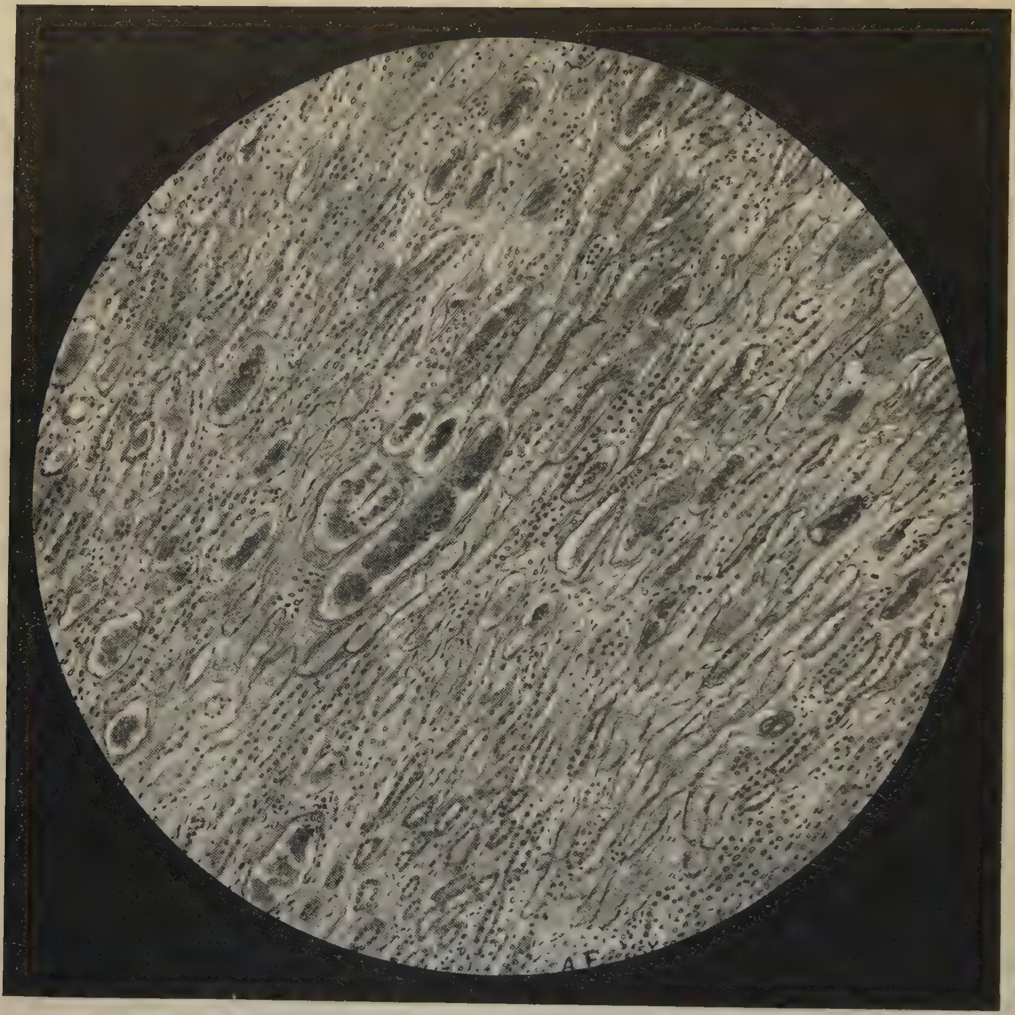

Plate XCVIII

Case xxi. Hemorrhagic Bright's disease, terminal stage.

A portion of the medulla is shown. The ducts of Bellini and larger collecting tubules are filled with broad large renal failure casts. Their mixed structure and fragile nature is evident. In some tubules the debris is still so loosely patched that it can hardly be considered a cast in the strict sense of the word. (Cf. Fig. 11, 17 Plates xxi a and b, lxxxvii.)

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AUG 13 1966	NOV 17 1966
FEB 22 1967	FEB 15 1967
MAY 28 1969	MAY 21 1969 B
JAN 06 2000	
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